Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Life Sciences 73 (2003) 3313–3321
Life Sciences
www.elsevier.com/locate/lifescie

Vitamin D receptor gene polymorphism is associated with chronic periodontitis

Yoichi Tachi[a,b,*], Hitomi Shimpuku[b], Yasuhiro Nosaka[c], Tatsuya Kawamura[d], Mitsuko Shinohara[b], Masatoshi Ueda[e], Hisao Imai[e], Kiyoshi Ohura[b]

[a] *Department of Food and Nutrition, Toita Women's College, Hachioji, Tokyo, Japan*
[b] *Department of Pharmacology, Osaka Dental University, Hirakata, Osaka, Japan*
[c] *Department of Dentistry and Oral-Maxillofacial Surgery, Kobe Nishi City Hospital, Kobe, Hyogo, Japan*
[d] *Kawamura Dental Clinic, Osaka, Osaka, Japan*
[e] *Department of Periodontology, Osaka Dental University, Hirakata, Osaka, Japan*

Received 15 August 2002; accepted 6 March 2003

Abstract

Chronic periodontitis (CP) is caused by enhanced resorption of the alveolar bone supporting the teeth and is associated with intraoral inflammation after infection with certain bacteria. The VDR gene polymorphism was reported recently to be deeply related to the occurrence of tuberculosis and infection of chronic hepatitis B virus. This may be interpreted to indicate a close relationship between VDR gene polymorphism and the immunological action, because vitamin D activates monocytes, stimulates cell-mediated immunity, and suppresses lymphocyte proliferation. The purpose of the present study was to clarify whether polymorphisms in VDR gene exons are associated with the incidence of CP. A case-controlled study was performed on a group of 168 unrelated Japanese subjects whose ages ranged from 35 to 65 years. The *Taq* I polymorphism in the VDR gene was found to be associated significantly with CP ($X^2 = 4.48$, $P = 0.034$). We performed multiple logistic regression analyses on the TT genotype, which was found to be associated with CP, and on well-recognized risk factors, smoking and diabetes. The odds ratio (OR) for the genotype (TT/Tt) was 2.73 (95% CI 1.11-6.68, $P = 0.028$), being larger than the unadjusted value. This indicates that the VDR gene polymorphism (TT genotype) is a risk factor for CP, independently of smoking and diabetes.

Keywords: Chronic periodontitis; Polymorphism; Vitamin D receptor; Gene; Case-control study

* Corresponding author. Department of Food and Nutrition, Toita Women's College, 139, Inume-machi, Hachioji, Tokyo, 193-0802 Japan. Fax: +81-426-21-0290.
E-mail address: tachi@mt.toita.ac.jp (Y. Tachi).

0024-3205/$ - see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/j.lfs.2003.03.001

Introduction

Chronic periodontitis (CP) is one of the most common diseases prevalent throughout the world, and it is the main cause of tooth loss in the elderly. Therefore, in order to increase the quality of life of old people, elucidation of the pathogenesis of this disease is of considerable significance. CP is known to be caused by intraoral inflammation after infection with specific bacteria and enhanced resorption of the alveolar bone supporting the teeth (Haffajee and Socransky, 1994; Offenbacher, 1996). It is not clear yet, however, why some people are susceptible to CP and others are not. To clarify the difference in individual susceptibility to CP in adult population, searches for a susceptibility gene for CP in adult population have been made and genes encoding proteins responsible for immunity, such as interleukin-1 (Kornman et al., 1997; Gore et al., 1998; Mark et al., 2000; Shimpuku and Ohura, 2001) and immunoglobulin G Fc receptor (Kobayashi et al., 1997), have been hitherto reported to be the susceptibility genes. However, since these genes are not sufficient to explain all of the host factors for CP, which is a multi-factorial disease, the presence of a more cardinal susceptibility gene has been suggested.

Several years ago, polymorphism of the vitamin D receptor (VDR) gene, which was considered to regulate bone metabolism, aroused considerable interest as a risk factor for osteoporosis (Ferrari et al., 1995; Matsuyama et al., 1995; Tokita et al., 1996). The VDR gene polymorphism was reported recently to be deeply related to the occurrence of tuberculosis and infection of chronic hepatitis B virus (HBV) (Bellamy et al., 1999). This may be interpreted to indicate a close relationship between VDR gene polymorphism and the immunological action, because the active hormonal form of 25-hydroxycholecalciferol, 1,25-dihydroxyvitamin D, activates monocytes, stimulates cell-mediated immunity, and suppresses lymphocyte proliferation.

In connection with the VDR gene, we have been interested in CP, the onset of which is triggered by reduced immunity against bacteria and enhanced bone resorption. It has been known that the VDR gene is located on chromosome 12, and that its polymorphism is detected by the presence or absence of a restriction site for *Fok* I in the translation initiation (ATG) site of exon 2 (Ames et al., 1999), as well as by that for *Bms* I and *Apa* I in intron 8 (Morrison et al., 1992), and by that for *Taq* I in exon 9 (Gennari et al., 1997; Ongphiphadhanakul et al., 1997). We have sought to examine whether two polymorphisms in exons of the VDR gene, that are recognized by restriction enzymes, *Taq* I and *Fok* I, are associated with the incidence of CP. For this purpose, we have performed a case-control study in a group of Japanese subjects.

Subjects and methods

Subjects

The subject group consisted of 168 unrelated Japanese volunteers from the Osaka Prefecture and was restricted to individuals aged between 35 and 65 years of age. The reason why we restricted ages of subjects like this was to minimize the effect of age that might obscure the influence of a predisposition reflecting the genotype of individuals. A control group containing young people in their teens and twenties did not seem to be appropriate for the present study, because they could have periodontitis at advanced ages. Conversely, a CP group containing patients over 65 did not seem appropriate, because it was possible that aging, rather than their predisposition, contributed more pronouncedly to the

occurrence of CP. Therefore, we selected subjects aged between 35 and 65 years. Written and oral informed consent was obtained from all subjects in accordance with the Helsinki Declaration of 1975 (revised in 2000). Subjects were screened according to the criteria of the World Health Organization (WHO) Community Periodontal Index of Treatment Needs (CPITN) (Ainamo et al., 1982). Ninety-four subjects meeting the criteria for Code 0 (no signs of disease) were assigned to a control group including 25 smokers and 4 diabetic patients (61 men, 33 women; mean age 45.5 [SD 6.8] years). From among patients meeting the criteria for Codes 1-4, 74 subjects who fulfilled the diagnostic criteria for CP defined by The American Academy of Periodontology in 1999 were selected to form the CP group including 28 smokers and 6 diabetic patients (43 men, 31 women; mean age 53.1 [SD 7.0] years). Persons who had smoked more than five cigarettes per day during the previous year were defined as smokers. For a diabetic diagnosis, the criteria of the WHO for diabetes mellitus were used.

DNA extraction and genotyping

DNA was isolated from peripheral leukocytes using a DNA extraction kit (Qiagen, Valencia, CA, USA). The polymorphisms defined by the restriction endonucleases *Taq* I and *Fok* I in the VDR gene were examined by the polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) method.

For the *Taq* I recognition site, PCR was carried out with 24 ng of genomic DNA, 0.5 U of *Taq* polymerase (TOYOBO, Japan) and the following oligonucleotide primers: 5′-CAGAGCATGGACAGG-GAGCAA-3′ and 5′-GCAACTCCTCATGGCTGAGGTCTC-3′. For optimal amplification, the Mg^{2+} concentration of the reaction buffer was adjusted to 1.5 mM. The PCR was performed in the GeneAmp PCR System 9700 (Applied Biosystems, USA). DNA was denatured at 95 °C for 15 min, followed by 33 cycles of denaturation at 94 °C for 30 seconds, annealing at 66 °C for 10 seconds and with extension at 74 °C for 30 seconds and a final extension step of 5 min. Following amplification, 3 μl of PCR product was digested with 10 units of *Taq* I restriction endonuclease at 65 °C for 3 h. The presence of a given restriction site was assigned by lower case and its absence by upper case (i.e. t and T for *Taq* I, respectively).

For the *Fok* I recognition site, PCR was carried out with 24 ng of genomic DNA, Ready-to-Go PCR Beads kit (Pharmacia, USA) and the following oligonucleotide primers: 5′-ATGGAAA-CACCTTGCTTCTTCTCCCC-3′ and 5′ –AGCTGGCCCTGGCACTGACT-CTGCCT-3′. For optimal amplification, the Mg^{2+} concentration of the reaction buffer was adjusted to 1.5 mM. DNA was denatured at 95 °C for 15 min, followed by 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 60 °C for 20 seconds and with extension at 74 °C for 50 seconds and a final extension step of 5 min. Following amplification, 3 μl of PCR product was digested with 10 units of *Fok* I restriction endonuclease at 37 °C for 2 h. The presence of a given restriction site was assigned by lower case and its absence by upper case (i.e., f and F for *Fok* I, respectively). The digested product was visualized after electrophoresis on a 10% polyacrylamide gel by ethidium bromide staining.

Multivariate logistic regression analyses

Since the pathogenesis of CP is multi-factorial, environmental factors cannot be neglected. In the present study, therefore, multiple logistic regression analyses to control for potential confounding effects of two notorious risk factors, smoking and diabetes was conducted.

Table 1
Distribution of VDR genotypes and alleles in patients with chronic periodotitis and controls

Taq I		Genotype		Odss ratio (95% CI)	p
		TT	Tt		
	Periodontitis (n=74)	66 (89.2%)	8 (10.8%)	2.52 (1.05–6.05)	0.034
	Control (n=94)	72 (76.6%)	22 (23.4%)		
		allele		Odds ratio (95% CI)	p
		T	t		
	Periodontitis (n=74)	140 (94.6%)	8 (5.4%)	2.32 (1.001–5.37)	0.045
	Control (n=94)	166 (88.3%)	22 (11.7%)		
Fok I		genotype			p
		FF	Ff	ff	
	Periodontitis (n=74)	28 (37.8%)	35 (47.3%)	13 (14.9%)	0.58
	Control (n=94)	43 (45.7%)	38 (40.4%)	11 (13.8%)	
		allele		Odds ratio (95% CI)	p
		F	f		
	Periodontitis (n=74)	91 (61.5%)	57 (38.5%)	1.21 (0.78–1.90)	0.40
	Control (n=94)	124 (66.0%)	64 (34.0%)		

Statistical analysis

Differences in prevalence of the genotypes between adult periodontitis patients and controls were tested using the χ^2-test. Differences were considered to be statistically significant at a level of $P < 0.05$.

Results

As shown in Table 1, the *Taq* I TT genotype in VDR gene polymorphism was found to be associated significantly with CP ($X^2 = 4.48$, P = 0.034). The T allele was also found to be associated significantly with CP ($X^2 = 4.04$, P = 0.045). Interestingly, the tt genotype was absent in the 168

Table 2
Relative risk for chronic periodontitis

	OR	95%CI	p-value
Vitamin D receptor genotype (TT/Tt)	2.73	1.11–6.68	0.028
Diabetes (yes/no)	2.25	0.58–8.76	0.24
Smoking (yes/no)	1.71	0.87–3.34	0.12

Multivariate logistic regression analyses were performed. Vitamin D receptor *Taq* I genotype contributed to the pathogenesis of chronic periodontitis with a relative risk of 2.73 (95% CI: 1.11 to 6.68), independently of other known risk factors for chronic periodontitis.

Japanese examined. For the *Fok* I polymorphism, neither genotype nor allele was found to be associated with CP.

Next, we performed multiple logistic regression analyses on the TT genotype, which was found to be associated with CP, and on well-recognized risk factors, smoking and diabetes. The odds ratio (OR) for the genotype (TT/Tt) was 2.73 (95% CI 1.11-6.68, P = 0.028), being larger than the unadjusted value. This indicates that VDR gene polymorphism (TT genotype) is a risk factor for CP, independently of smoking and diabetes (Table 2). The ORs for smoking and diabetes were 1.71 (0.87–3.34, P = 0.12) and 2.25 (0.58–8.76, P = 0.24), respectively.

Discussion

1,25-Dihydroxyvitamin D, an active form of vitamin D, not only plays an essential role in bone metabolism, but also facilitates phagocytosis by monocytes (Rook et al., 1986; Rockett et al., 1998) as well as monocyte differentiation (Zhang et al., 1994), thereby exerting a great influence on the immune function. These biological actions of 1,25-dihydroxyvitamin D results from its binding to VDR. Since the main cause of CP is inflammation after bacterial infection that enhances resorption of the alveolar bone (Haffajee and Socransky, 1994; Offenbacher, 1996), the VDR gene seems to be a reasonable candidate for the CP-susceptibility gene. We have studied, therefore, the association of polymorphism in exons of the VDR gene with CP.

In this study, we found a significant association between the *Taq* I polymorphism in the VDR gene and the incidence of CP. The TT genotype and the T allele were found to be associated with CP. The TT genotype is identical with that reported to be associated with the occurrence of tuberculosis and infection of chronic HBV (Bellamy et al., 1999). These findings suggest that the TT genotype and the T allele lead to an increase in the susceptibility of individuals not only to CP, tuberculosis and hepatitis B but also to other infectious diseases. We think therefore that the association of the VDR gene polymorphism with other infectious diseases should be examined.

This study of Japanese subjects provides the first demonstration of an association between VDR gene polymorphism and CP. In the literature on periodontitis, VDR gene polymorphism was reported to be associated with the incidence of early-onset periodontitis (EOP) and localized early-onset periodontitis (L-EOP). The study on EOP was made by us in Chinese subjects (Sun et al., 2002), while that on L-EOP was made in Caucasians by an English group (Hennig et al., 1999). It is interesting to note that the *Taq* I polymorphism in the VDR gene associated with EOP and L-EOP was of the tt genotype and t allele, the opposite to that found to be associated with CP in the present study. A possible explanation for these opposite findings may be sought in the ethnic difference. The prevalence of many genotype is completely different in populations like Japanese and Caucasians, for example in the interleukin-1 (Kornman et al., 1997; Tai et al., 2002), interleukin-10 (Yamazaki et al., 2001), Fcγ receptor genes (Kobayashi et al., 2001; Meisel et al., 2001). However, Chinese, in which we studied previously the association between EOP and VDR gene polymorphism, are racially similar to Japanese. Therefore, the explanation that the inconsistent findings resulted from the ethnic difference does not seem to be plausible. The tt genotype and t allele were reported to be associated with decreases in bone-mineral density (BMD) and the incidence of osteoporosis (Spector et al., 1995; Zmuda et al., 1997). The *Taq* I polymorphism in the VDR gene can have influences on both the immune function and bone resorption. It is possible that the influence on bone resorption contributes more effectively to cause EOP, whereas the influence on the immune function

contributes more effectively to cause CP. The mechanism of the occurrence of CP has been presumed to be different from that of EOP. The present finding may be taken to support this presumption.

In the literature, there are reports of two studies in which the association between VDR gene polymorphism and periodontitis was examined in adults. One was our study in Chinese subjects (Sun et al., 2002), and the other was that of Yoshimura et al. in Japanese subjects (Yoshihara et al., 2001). In disagreement with the present study, no significant association was found between the *Taq* I polymorphism in the VDR gene and periodontitis in those two studies. Why are results of the present study inconsistent with those of the previous studies? As a possible explanation, it may be considered that the amount of ingestion of vitamin D and/or the serum concentration of vitamin D might be different between the subjects in the present study and those in the preceding studies. While studying the relationship between the VDR gene polymorphism and the serum concentration of vitamin D in tuberculosis, Wilkinson et al. found the association between the TT genotype and tuberculosis only in a group with vitamin D deficiency (Wilkinson et al., 2000). Namely, the association between the *Taq* I polymorphism and the occurrence of an infectious disease can be either obscured at high serum vitamin D concentrations as reported by Wilkinson et al. or revealed independently of other factors as reported by Bellamy (Bellamy et al., 1999). A phenomenon similar to that found by Wilkinson et al. was noted in a study on the relationship between the VDR gene polymorphism and osteoporosis. Kiel et al. examined the relationship of the amount of Ca ingestion and the VDR gene polymorphism with bone mineral density, and reported that the association of the VDR gene polymorphism with bone mineral density was either disclosed or obscured depending on the amount of Ca ingestion (Kiel et al., 1997). Stated in other words, when the relationship between the VDR gene polymorphism and bone mineral density is studied in two subject groups having different amounts of Ca ingestion, results obtained from these two groups may be inconsistent. In view of the findings of Wilkinson et al. and Kiel et al., the possibility cannot be easily excluded that the inconsistency between the results of the present study and those of the preceding studies was due to differences in a nutritional factor, such as the amount of vitamin D ingested by the subjects among different studies.

In this paragraph, we like to describe a methodological revision made in the present study in comparison with the two preceding studies in which the association between the VDR gene polymorphism and periodontitis was examined in adults. We think that the age of members in the control group was not sufficiently restricted in our previous study in Chinese(Sun et al., 2002) and that of Yoshimura et al. in Japanese subjects(Yoshihara et al., 2001). In these two studies, control groups included young members in their teens and twenties. Such control groups are not appropriate because the possibility can not be excluded that these young subjects have periodontitis when they get older, for example at 35 years of age. In the present study, therefore, we had a control group consisting of members over 35. Although there is no age limit in the diagnostic criteria of CP, a tacit rule will be probably necessary hereafter that ‘the youngest subjects in control group should be older than those accepted usually at present’, when the association between CP and gene polymorphism is examined.

The mechanism by which VDR gene polymorphism influences the incidence of CP has not been clarified. The VDR gene is located on chromosome 12, and the *Taq* I polymorphism is located in exon 9. Although this region does not code for amino acids directly, polymorphism in this region has been reported to be correlated with the length of poly(A) in the 3′-untranslated region (3’-UTR) (Ingles et al., 1997). In view of this report, it is no wonder that polymorphism in this region contributes to functional differences. *Fok* I polymorphism, associated with decreased bone-mineral density (BMD), results from a

C-to-T transition that creates an alternative initiation codon (ATG) three codons from the downstream start site (Gross et al., 1996). In our study, *Fok* I polymorphism was not found to be associated with CP, however. The possibility that *Fok* I polymorphism in the VDR gene influences the incidence of CP seems to be low.

The influence of numerous risk factors is presumed for CP, a multi-factorial disease. Among them, smoking is a well-known major risk factor (Grossi et al., 1995; Kaldahl et al., 1996; Kornman and Giovine, 1998; Tonetti, 1998). In exploration of the susceptibility gene for periodontitis, it was assumed that the effect of smoking obscured the influence of genetic polymorphism. In fact, a significant association was occasionally revealed by analyses in subject groups consisting of nonsmokers alone (Kornman et al., 1997; McDevitt et al., 2000). In the present study of Japanese subjects, however, a significant association was found between CP and genetic polymorphism, even though the subjects included smokers. The *Taq* I polymorphism in the VDR gene probably exerts a more marked influence on the occurrence of CP than do the other susceptibility genes reported previously. Performing multiple logistic regression analyses on the TT genotype, which was found to be associated significantly with CP, and on smoking and diabetes, we found that odds ratio (OR) for the genotype (TT/Tt) was 2.73 (95% CI 1.11-6.68, P = 0.028), being larger than the unadjusted value. This indicates that VDR gene polymorphism (TT genotype) is a risk factor for CP, independently of smoking and diabetes (Table 2). The fact that the OR for the TT genotype (2.73) was larger than ORs for smoking (1.71) and diabetes (2.25) suggests that the VDR gene polymorphism can predict the occurrence of CP more accurately than the risk factors reported previously.

In the last several years, reports concerning the susceptibility gene for CP have been accumulating as follows; interleukin-1 (Kornman et al., 1997; Gore et al., 1998; Mark et al., 2000; Shimpuku and Ohura, 2001), receptor for advanced glycation end products (Holla et al., 2001), plasminogen-activator-inhibitor-1 (Holla et al., 2002) and immunoglobulin G Fc receptor (Kobayashi et al., 1997). However, the search for the susceptibility gene for CP is rather poorly developed in comparison with that for other multi-factorial diseases such as diabetes and hypertension. Further studies that include the bacterial infection as well as to bone metabolism should be performed. After susceptibility genes for CP are finally listed up, the influence of combinations of these genes on the occurrence of periodontitis will be examined in the next step.

Acknowledgements

This work was supported in part by grant for the Science Research Promotion Fund of the Promotion and Mutual Aid Corporation for Private Schools of Japan. We are grateful to Professor Naochika Domae and Professor Kenji Kakudo for helpful suggestions. We thank the members of the Kawamura Dental Clinic for cooperation in the provision of samples. This study was performed with the assistance of the Institute of Dental Research, Osaka Dental University.

References

Ainamo, J., Barmes, D., Beagrie, G., Cutress, T., Martin, J., Sardo-Infirri, J., 1982. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). International Dental Journal 32 (3), 281–291.

Ames, S.K., Ellis, K.J., Gunn, S.K., Copeland, K.C., Abrams, S.A., 1999. Vitamin D receptor gene Fok1 polymorphism predicts calcium absorption and bone mineral density in children. Journal of Bone and Mineral Research 14 (5), 740–746.

Bellamy, R., Ruwende, C., Corrah, T., McAdam, K.P., Thursz, M., Whittle, H.C., Hill, A.V., 1999. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. Journal of Infectious Diseases 179 (3), 721–724.

Ferrari, S., Rizzoli, R., Chevalley, T., Slosman, D., Eisman, J.A., Bonjour, J.P., 1995. Vitamin-D-receptor-gene polymorphisms and change in lumbar-spine bone mineral density. Lancet 345 (8947), 423–424.

Gennari, L., Becherini, L., Masi, L., Gonnelli, S., Cepollaro, C., Martini, S., Mansani, R., Brandi, M.L., 1997. Vitamin D receptor genotypes and intestinal calcium absorption in postmenopausal women. Calcified Tissue International 61 (6), 460–463.

Gore, E.A., Sanders, J.J., Pandey, J.P., Palesch, Y., Galbraith, G.M., 1998. Interleukin-1beta + 3953 allele 2: association with disease status in adult periodontitis. Journal of Clinical Periodontology 25 (10), 781–785.

Gross, C., Eccleshall, T.R., Malloy, P.J., Villa, M.L., Marcus, R., Feldman, D., 1996. The presence of a polymorphism at the translation initiation site of the vitamin D receptor gene is associated with low bone mineral density in postmenopausal Mexican-American women [see comments]. Journal of Bone and Mineral Research 11 (12), 1850–1855.

Grossi, S.G., Genco, R.J., Machtei, E.E., Ho, A.W., Koch, G., Dunford, R., Zambon, J.J., Hausmann, E., 1995. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. Journal of Periodontology 66 (1), 23–29.

Haffajee, A.D., Socransky, S.S., 1994. Microbial etiological agents of destructive periodontal diseases. Periodontology 2000 (5), 78–111.

Hennig, B.J., Parkhill, J.M., Chapple, I.L., Heasman, P.A., Taylor, J.J., 1999. Association of a vitamin D receptor gene polymorphism with localized early-onset periodontal diseases. Journal of Periodontology 70 (9), 1032–1038.

Holla, L.I., Kankova, K., Fassmann, A., Buckova, D., Halabala, T., Znojil, V., Vanek, J., 2001. Distribution of the receptor for advanced glycation end products gene polymorphisms in patients with chronic periodontitis: a preliminary study. Journal of Periodontology 72 (12), 1742–1746.

Holla, L.I., Buckova, D., Fassmann, A., Benes, P., Znojil, V., 2002. Plasminogen-activator-inhibitor-1 promoter polymorphism as a risk factor for adult periodontitis in non-smokers. Genes Immun. 3 (5), 292–294.

Ingles, S.A., Haile, R.W., Henderson, B.E., Kolonel, L.N., Nakaichi, G., Shi, C.Y., Yu, M.C., Ross, R.K., Coetzee, G.A., 1997. Strength of linkage disequilibrium between two vitamin D receptor markers in five ethnic groups: implications for association studies. Cancer Epidemiology, Biomarkers and Prevention 6 (2), 93–98.

Kaldahl, W.B., Johnson, G.K., Patil, K.D., Kalkwarf, K.L., 1996. Levels of cigarette consumption and response to periodontal therapy. Journal of Periodontology 67 (7), 675–681.

Kiel, D.P., Myers, R.H., Cupples, L.A., Kong, X.F., Zhu, X.H., Ordovas, J., Schaefer, E.J., Felson, D.T., Rush, D., Wilson, P.W., Eisman, J.A., Holick, M.F., 1997. The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density. Journal of Bone and Mineral Research 12 (7), 1049–1057.

Kobayashi, T., Westerdaal, N.A., Miyazaki, A., van der Pol, W.L., Suzuki, T., Yoshie, H., van de Winkel, J.G., Hara, K., 1997. Relevance of immunoglobulin G Fc receptor polymorphism to recurrence of adult periodontitis in Japanese patients. Infection and Immunity 65 (9), 3556–3560.

Kobayashi, T., Yamamoto, K., Sugita, N., van der Pol, W.L., Yasuda, K., Kaneko, S., van de Winkel, J.G., Yoshie, H., 2001. The Fc gamma receptor genotype as a severity factor for chronic periodontitis in Japanese patients. Journal of Periodontology 72 (10), 1324–1331.

Kornman, K.S., Giovine, F.S., 1998. Genetic variations in cytokine expression: a risk factor for severity of adult periodontitis. Annals of Periodontology 3 (1), 327–338.

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

Mark, L.L., Haffajee, A.D., Socransky, S.S., Kent, R.L., Guerrero, D., Kornman, K., Newman, M., Stashenko, P., 2000. Effect of the interleukin-1 genotype on monocyte IL-1beta expression in subjects with adult periodontitis. Journal of Periodontal Research 35 (3), 172–177.

Matsuyama, T., Ishii, S., Tokita, A., Yabuta, K., Yamamori, S., Morrison, N.A., Eisman, J.A., 1995. Vitamin D receptor genotypes and bone mineral density. Lancet 345 (8959), 1238–1239.

McDevitt, M.J., Wang, H.Y., Knobelman, C., Newman, M.G., di Giovine, F.S., Timms, J., Duff, G.W., Kornman, K.S., 2000. Interleukin-1 genetic association with periodontitis in clinical practice. Journal of Periodontology 71 (2), 156–163.

Meisel, P., Carlsson, L.E., Sawaf, H., Fanghaenel, J., Greinacher, A., Kocher, T., 2001. Polymorphisms of Fc gamma-receptors RIIa, RIIIa, and RIIIb in patients with adult periodontal diseases. Genes Immun. 2 (5), 258–262.

Morrison, N.A., Yeoman, R., Kelly, P.J., Eisman, J.A., 1992. Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proceedings of the National Academy of Sciences of the United States of America 89 (15), 6665–6669.

Offenbacher, S., 1996. Periodontal diseases: pathogenesis. Annals of Periodontology 1 (1), 821–878.

Ongphiphadhanakul, B., Rajatanavin, R., Chanprasertyothin, S., Chailurkit, L., Piaseu, N., Teerarungsikul, K., Sirisriro, R., Komindr, S., Puavilai, G., 1997. Vitamin D receptor gene polymorphism is associated with urinary calcium excretion but not with bone mineral density in postmenopausal women. Journal of Endocrinological Investigation 20 (10), 592–596.

Rockett, K.A., Brookes, R., Udalova, I., Vidal, V., Hill, A.V., Kwiatkowski, D., 1998. 1,25-Dihydroxyvitamin D3 induces nitric oxide synthase and suppresses growth of Mycobacterium tuberculosis in a human macrophage-like cell line. Infection and Immunity 66 (11), 5314–5321.

Rook, G.A., Steele, J., Fraher, L., Barker, S., Karmali, R., O'Riordan, J., Stanford, J., 1986. Vitamin D3, gamma interferon, and control of proliferation of Mycobacterium tuberculosis by human monocytes. Immunology 57 (1), 159–163.

Shimpuku, H., Ohura, K., 2001. Association of interleukin-1 gene polymorphisms with adult periodontitis in Japanese. Journal of Osaka Dental University 35, 99–104.

Spector, T.D., Keen, R.W., Arden, N.K., Morrison, N.A., Major, P.J., Nguyen, T.V., Kelly, P.J., Baker, J.R., Sambrook, P.N., Lanchbury, J.S., et al., 1995. Influence of vitamin D receptor genotype on bone mineral density in postmenopausal women: a twin study in Britain. BMJ 310 (6991), 1357–1360.

Sun, J.L., Meng, H.X., Cao, C.F., Tachi, Y., Shinohara, M., Ueda, M., Imai, H., Ohura, K., 2002. Relationship between vitamin D receptor gene polymorphism and periodontitis. Journal of Periodontal Research 37 (4), 263–267.

Tai, H., Endo, M., Shimada, Y., Gou, E., Orima, K., Kobayashi, T., Yamazaki, K., Yoshie, H., 2002. Association of interleukin-1 receptor antagonist gene polymorphisms with early onset periodontitis in Japanese. Journal of Clinical Periodontology 29 (10), 882–888.

Tokita, A., Matsumoto, H., Morrison, N.A., Tawa, T., Miura, Y., Fukamauchi, K., Mitsuhashi, N., Irimoto, M., Yamamori, S., Miura, M., Watanabe, T., Kuwabara, Y., Yabuta, K., Eisman, J.A., 1996. Vitamin D receptor alleles, bone mineral density and turnover in premenopausal Japanese women. Journal of Bone and Mineral Research 11 (7), 1003–1009.

Tonetti, M.S., 1998. Cigarette smoking and periodontal diseases: etiology and management of disease. Annals of Periodontology 3 (1), 88–101.

Wilkinson, R.J., Llewelyn, M., Toossi, Z., Patel, P., Pasvol, G., Lalvani, A., Wright, D., Latif, M., Davidson, R.N., 2000. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet 355 (9204), 618–621.

Yamazaki, K., Tabeta, K., Nakajima, T., Ohsawa, Y., Ueki, K., Itoh, H., Yoshie, H., 2001. Interleukin-10 gene promoter polymorphism in Japanese patients with adult and early-onset periodontitis. Journal of Clinical Periodontology 28 (9), 828–832.

Yoshihara, A., Sugita, N., Yamamoto, K., Kobayashi, T., Miyazaki, H., Yoshi, H., 2001. Analysis of vitamin D and Fcgamma receptor polymorphisms in Japanese patients with generalized early-onset periodontitis. Journal of Dental Research 80 (12), 2051–2054.

Zhang, D.E., Hetherington, C.J., Gonzalez, D.A., Chen, H.M., Tenen, D.G., 1994. Regulation of CD14 expression during monocytic differentiation induced with 1 alpha,25-dihydroxyvitamin D3. Journal of Immunology 153 (7), 3276–3284.

Zmuda, J.M., Cauley, J.A., Danielson, M.E., Wolf, R.L., Ferrell, R.E., 1997. Vitamin D receptor gene polymorphisms, bone turnover, and rates of bone loss in older African-American women. Journal of Bone and Mineral Research 12 (9), 1446–1452.