J Clin Periodontol 2006; 33: 524–528 doi: 10.1111/j.1600-051X.2006.00944.x

Journal of Clinical Periodontology

The short vitamin D receptor is associated with increased risk for generalized aggressive periodontitis

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Park KS, Nam JH, Choi J. The short vitamin D receptor is associated with increased risk for generalized aggressive periodontitis. J Clin Periodontol 2006; 33: 524–528. doi: 10.1111/j.1600-051X.2006.00944.x.

Abstract

Background: Generalized aggressive periodontitis (GAP) exhibits severe inflammation and alveolar bone loss. Vitamin D receptor (VDR) regulates both bone metabolism and inflammation-related genes, and its polymorphisms and haplotypes may affect the functional activity of the VDR protein in GAP.

Objective: We analysed the genetic effect of *VDR* start codon, intron, and exon polymorphisms, and their haplotypes on the development of GAP.

Materials and Methods: The *VDR* start codon *27823C>T* (rs2228570, *Fok*I), intron 8 *60890G>A* (rs154410, *Bsm*I), and exon 9 *61968T>C* (rs731236, *Taq*I) polymorphisms were determined by using the polymerase chain reaction–restriction fragment length polymorphism analysis among 93 GAP patients and 143 healthy controls.

Results: The *VDR* start codon *27823*C/*C* genotype was associated with an increased risk for GAP [odds ratio (OR) = 1.83, $p = 0.028$], but the intron 8 *60880G>A* and exon 9 *61968T>C* polymorphisms were not associated with GAP. The *VDR* haplotype homozygote *ht1*(*C–G–T*) carrying *27823*C* allele was associated with a 1.8-fold increased risk of GAP (OR = 1.84, $p = 0.030$).

Conclusion: These results demonstrate that the short VDR (*27823*C/*C*) protein may influence GAP susceptibility.

Key words: generalized aggressive periodontitis; polymorphism; vitamin D receptor

Accepted for publication 10 April 2006

Generalized aggressive periodontitis (GAP) is an inflammatory disease, which has its onset primarily during early adult years. GAP is characterized by the rapid, severe destruction of periodontal tissue, including the alveolar bone (Armitage 2004, van der Velden 2005). Although the aetiology of GAP has previously been associated with periodontopathogenic bacteria, and this may indeed constitute an initiator of the condition, its clinical features have been shown to result from several genetic and environmental factors (Page et al. 1997, Kinane et al. 2005).

The vitamin D receptor (VDR) is involved in a variety of biological processes, including bone metabolism and the modulation of the immune response, a role in which it functions as a vitamin D_3-dependent transcription factor (Uitterlinden et al. 2004). VDR is also an important nuclear receptor of vitamin D_3, which is known to be essential for the maintenance of mineral homeostasis and for bone structural integrity. Vitamin D_3 and its receptor have also been demonstrated to act as up-regulating agents during innate immunity, via the enhancement of phagocytosis by monocytes/macrophages (Selvaraj et al. 2004). VDR exerts an effect on potent osteoclastogenic cytokines, including interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-α in macrophage mRNA synthesis in vitro (Graves & Cochran 2003, Zittermann 2003). VDR mediates these effects via a variety of mechanisms, including transcription regulation, mRNA stability, post-translational modifications, and ligand-induced stabilization of the gene products.

The *VDR* (OMIM 601769) gene on 12q13 harbours eight exons that are invariably translated, and six that are alternatively spliced. The *VDR* gene exhibits several polymorphisms, located in both the coding and the non-coding portions of the gene. The *27823C>T* polymorphism in exon 2, which is located eight nucleotides upstream of the initiation start site, creates an additional

start codon (ACG to ATG), thus forming a protein three amino acids longer than the original. Therefore, this polymorphism can generate either a short protein of 424 amino acids (*C27823*) or a long protein of 427 amino acids (*27823T*), and the short VDR is 1.5–2.5-fold more transcriptionally active than the long VDR variant. The most significant difference between the two results when these isoforms are assayed in osteoblast-like cells that use a vitamin D response element in their natural bone-specific promoters (Jurutka et al. 2000, Whitfield et al. 2001). The 3′ untranslated region polymorphisms are situated in intron 8 (*60890G>A*) and an adjacent site within exon 9 (*61968T>C*; *Ile352Ile*). These *VDR* polymorphisms have been shown to alter both the expression levels and the mRNA stability of VDR, and can thus be considered positional candidates for several complex diseases, including GAP (Yoshihara et al. 2001), chronic periodontitis (Sun et al. 2002, Tachi et al. 2003), osteoporosis (Gennari et al. 2002), and osteoarthritis (Uitterlinden et al. 1997). Previous studies have also evaluated the association between GAP and polymorphisms in the genes encoding for IL-1, TNF-α, and Fcγ receptors (Loos et al. 2005).

In this study, we investigated the genetic effects of the *VDR* start codon, intron, and exon polymorphisms, as well as their haplotypes, with regard to susceptibility to GAP.

Materials and Methods

Subjects

The study population comprised 93 GAP patients and 143 periodontally healthy controls. None of all the GAP patients and controls had systemic diseases such as diabetes mellitus or polymorphonuclear defects, which correlate with the destructive periodontal disease, and pregnant subjects were also excluded. All subjects who participated in this study were of Korean ethnicity. The Institutional Review Board of Pusan National University Hospital approved the study protocol, and a written informed consent was obtained from each subject.

GAP was diagnosed on the basis of clinical attachment loss and radiographic patterns of alveolar bone loss by using the criteria defined by the American Academy of Periodontology (Armitage 1999). The patients enrolled had a clinical attachment loss of ⩾6 mm affecting 10 or more teeth, at least three of which were not first molars or incisors. The GAP patient group contained 59 males and 34 females with a mean age of 35 ± 6.4 years. The age at diagnosis for GAP was considerably younger in most cases and below 35 years in all cases. The healthy control group did not have pocket-probing depth >4 mm, and there were no sites with radiographic evidence of bone loss. The control group contained 103 males and 40 females with a mean age of 25 ± 2.6 years.

Genotype analysis

Genomic DNA was isolated from peripheral blood leucocytes with a QIA amp DNA Blood Kit (Qiagen, Hilden, Germany). Three single-nucleotide polymorphisms (SNPs) of the *VDR* gene at the following positions (according to GenBank accession No. AY342401): *27823T>C* (rs2228570, *Fok*I), *60890G>A* (rs154410, *Bsm*I), and *61968T>C* (rs731236, *Taq*I) were analysed by the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). The *27823T>C* was amplified with PCR using primers 5′-AGCTG GCCCTGGCACTGA CTCTGCTCT-3′ and 5′-ATG GAAACACCTTGCTTC TTCTCCCTC-3′ and digested with the *Fok*I restriction enzyme (Arai et al. 1997, Ingles et al. 2001). The *60890G>A* was amplified by using primers 5′-GAGCC CAGTTCACGCAAGAG-3′ and 5′-GG GGGGA TTCTGAGGAACTAGATA-3′ and was digested with the *Bsm*I restriction enzyme (Kim et al. 2001). The *61968T>C* was amplified by using primers 5′-CAGAGCATGGACAGGGAG CAAG-3′ and 5′-GCAACTCCTCATG GGCT GAGGTCTCA-3′ and was digested with *Taq*I (Curran et al. 1999). The digested PCR products were electrophoresed on an 8% (*Fok*I and *Bsm*I) or 5% (*Taq*I) polyacrylamide gel and were stained with ethidium bromide to visualize DNA fragments.

Statistical analysis

The deviations of genotype distribution from Hardy–Weinberg equilibrium and degree of pairwise linkage disequilibria were estimated by using the R program v.1.9.1 (http://cran.r-project.org). Haplotype frequencies were inferred by using the PHASE program (http://www.stat.washington.edu/stephens/phase.html). The genotypic and allelic frequencies of SNPs for GAP patients and healthy controls were compared by using the χ^2 test (2 × 3, 2 × 2). Also, the haplotypic frequencies for patients and healthy controls were compared by using the χ^2 test (2 × 2). The odds ratios (ORs), 95% confidence intervals (CIs), and significance were calculated by using SAS v8.1e (SAS Institute, Cary, NC, USA). Corrected p vaules were calculated for multiple testing by the Bonferroni method. Statistical significance in all tests was $p<0.05$.

Results

Association analysis of *VDR* polymorphisms

The genotypic distributions of the three SNPs, *VDR 27823C>T*, *60890G>A*, and *61968T>C*, were consistent with Hardy–Weinberg equilibrium for the controls and patients. Genotypic (2 × 3) and allelic frequencies involving *VDR 27823C>T* evidenced no differences between the patients and the controls. However, the *VDR 27823*C/*C* genotype was detected with a significantly higher frequency in the GAP patients than in the healthy controls, according to the χ^2 test (**C/*C versus *C/*T+*T/*T*, OR = 1.83%, 95% CI = 1.06–3.16, $p = 0.028$) (Table 1). Genotypic (2 × 3, 2 × 2) and allelic frequencies involving *VDR 60890G>A* (*Bsm*I) and *61968T>C* (*Taq*I) also evidenced no differences between patients and controls.

Among estimated eight haplotypes of *VDR C27823T–G60890A–T61968C* localized on 12q13, three common haplotypes with frequency >0.01 were compared between GAP patients and healthy controls by using χ^2 analysis (Table 1). The haplotype *ht1*(*C–G–T*) homozygote frequency carrying the *27823*C* allele was found to be significantly higher in patients than in controls (OR = 1.84, 95% CI = 1.06–3.20, $p = 0.030$).

Among the control group, *VDR 27823C>T* SNP was found to have no linkage disequilibrium (LD) with *60890 G>A* and *61968T>C* in an adjacent site of 3′ untranslated region ($r^2<0.03$), whereas *60890 G>A* showed to have LD with *61968T>C* ($r^2>0.5$, Table 2).

Discussion

Periodontal diseases are characterized by chronic inflammatory disease and,

Table 1. Genotype and allele frequencies of *VDR* polymorphisms in generalized aggressive periodontitis (GAP) patients and healthy controls

SNP		GAP ($n = 93$)	Controls ($n = 143$)	OR	95% CI	p
27823 C>T	**C/*C*	41 (44.1)	43 (30.1)	1.83	1.06–3.16	0.028†
(C*1Met*)	**C/*T*	38 (40.9)	75 (52.4)			
rs2228570	**T/*T*	14 (15.0)	25 (17.5)			
	**C*	0.645	0.563			
60890 G>A	**G/*G*	87 (93.5)	134 (93.7)			
rs154410	**G/*A*	6 (6.5)	9 (6.3)			
	**A/*A*	0 (0.0)	0 (0.0)			
	**A*	0.032	0.031			
61968 T>C	**T/*T*	86 (92.5)	133 (93.0)			
(*Ile352Ile*)	**T/*C*	7 (7.5)	10 (7.0)			
rs731236	**C/*C*	0 (0.0)	0 (0.0)			
	**C*	0.038	0.035			
Haplotype *VDR C27823T–G60890A–T61968C*‡						
ht1 C–G–T	*ht1/ ht1*	38 (40.9)	39 (27.3)	1.84	1.06–3.20	0.030§
	ht1/ –	37 (39.8)	71 (49.7)			
	– / –	18 (19.3)	33 (23.0)			
ht1 C–G–T		0.612	0.528			
ht2 T–G–T		0.350	0.430			
ht3 C–A–C		0.027	0.020			
Others		0.011	0.022			

†χ^2 analysis (**C/*C versus *C/*T + *T/*T*).
‡Haplotypes with frequency >0.01 were presented out of eight haplotypes estimated.
§χ^2 analysis (*ht1/ ht1 versus ht1/ – + – / –*).
VDR, vitamin D receptor; SNP, single-nucleotide polymorphism.

Table 2. Linkage disequilibrium coefficient (r^2) among *VDR* SNP loci in the Korean population

SNP		*27823C>T*	*60890G>A* r^2	*61968T>C*
27823C>T		–	0.025	0.028
60890G>A	p	0.008	–	0.527
61968T>C		0.005	<0.001	–

VDR, vitamin D receptor; SNP, single-nucleotide polymorphism.

ultimately, the progression of tooth loss. In particular, the primary clinical feature of GAP is rapid and severe irreversible alveolar bone loss. The GAP patient group evaluated in this study consisted of more severe patients, who exhibited a clinical attachment loss of ⩾6 mm affecting ⩾10 teeth at primary dentition. In addition, these patients evidence more clearly defined genetic factors than do patients with chronic periodontitis (Hodge & Michalowicz 2001).

In this study, the short VDR, which harbours the *27823*C/*C* genotype, was associated with an increased risk of GAP. In a Japanese study involving chronic periodontitis patients, no such association was reported (Tachi et al. 2003). Several association studies involving *VDR 60890G>A* (*Bsm*I) in intron 8 and *61968T>C* (*Ile352Ile*, *Taq*I) in exon 9 have been conducted, using different ethnic populations for the patient groups. In our study, *VDR 60890G>A* evidenced no association with GAP, a finding similar to that previously reported in a study of a Japanese population (Yoshihara et al. 2001). The *VDR 60890G>A* variant allele was detected at a lower frequency among Koreans (3.1%) and Japanese (10.0%) than among Caucasians (31.2%) (Yoshihara et al. 2001, Slattery et al. 2004). In association studies involving *61968T>C*, no associations were reported among Korean GAP patients and Caucasian aggressive periodontitis patients, which differs from the previous results obtained with a group of Chinese aggressive periodontitis patients (Hennig et al. 1999, Sun et al. 2002). The *VDR 61968*C* variant allele was detected with a significantly higher frequency among Chinese aggressive periodontitis patients than among the controls (12.2% *versus* 2.6%, OR = 5.26, $p = 0.022$). Among the controls, the frequency of the *VDR 61968*C* allele was found to be relatively low (2.6–11.7%) in Asians including Koreans, Chinese, and Japanese, but rather high (31.9%) in Caucasians (Hennig et al. 1999, Sun et al. 2002, Tachi et al. 2003). The *VDR* haplotype *ht1*(*C–G–T*) homozygote frequency, which harbours the risk allele *27823*C*, was associated with a high risk of GAP (OR = 1.84, $p = 0.030$). However, the haplotype *G–T* of *60890G>A* and *61968T>C* has been previously associated with Brazilian chronic periodontitis (de Brito Junior et al. 2004). One possible explanation for these inconsistent findings may lie in the observed differences in the disease phenotype, as well as in observed variations in the frequency of the *VDR* minor allele between ethnic groups.

In this study, *VDR 27823C>T* SNP was found to have no LD with *60890G>A* and *61968T>C* SNPs in the 3′ untranslated region. It has also been reported to have no LD with any of the other SNPs in the promoter and the 3′ untranslated regions (Fang et al. 2005). The start codon polymorphism is, therefore, unlikely to explain the association results of the *60890G>A* and *61968T>C* SNPs. Considering the relatively vast distance between the two sites (about 40 kb) and the structural differences between the polymorphisms, it appears that these two should be considered different markers (Uitterlinden et al. 2002).

In order to compensate for multiple testing, we utilized the Bonferroni correction, which caused the significant p value ($p > 0.01$) to disappear. This correction is known to be conservative, and thus may have effected an overcorrection of the raw p value.

The VDR functions as a 1, $25(OH)_2$ vitamin D_3-inducible trans-acting transcription factor. The short 424-amino acid VDR (*VDR 27823*C/*C* genotype) is able to interact more efficiently with the transcription factor TFII B in vitro, and also more efficiently transactivates vitamin D target genes than does the long 427-amino acid VDR (Jurutka et al. 2000, Whitfield et al. 2001, Uitterlinden et al. 2004). Thus, the short VDR appears to transmit stronger bone resorption and inflammation signals. VDR also appears to be vital to the ability of vitamin D_3 to elicit a signal from osteoblasts, which in turn

facilitates the in vitro differentiation of osteocytes, and also the ability of vitamin D_3 to reduce macrophage and lymphocyte function in vitamin D-deficient rats (Lemire 1995, Haussler et al. 1998). Serum levels of vitamin D have been shown to induce a suppression of the synthesis of cytokines such as IL-1, IL-6, and TNF-α, whereas low levels of vitamin D intake and calcium intake induce a low calcium serum level, which stimulates the parathyroid gland to generate the parathyroid hormone, which results in osteoclastogenesis (Hildebolt 2005). A statistically significant association has been detected between low serum calcium and periodontal disease in younger females (aged 20–39) with an OR = 6.11 (Nishida et al. 2000). Low dietary calcium intake has been reported to result in more severe periodontal disease. A number of infectious diseases have also been linked to low vitamin D levels. Owing to the unique periodontal-pathogen characteristics of periodontal disease, it has been reported that the effects of vitamin D and calcium on the alveolar bone are somewhat more pronounced than their effects on the spine and hip bones (Hildebolt 2005).

In summary, the results of this study indicate that the short VDR (*27823*C/*C* genotype) may have an influence on the risk of GAP, and may also have a significant role in the predisposition towards GAP.

Acknowledgement

This study was supported by a grant from Sungshin Women's University in 2004 (2004-1-11-012/1).

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Clinical Relevance

Scientific rationale: The primary clinical feature of GAP is severe alveolar bone loss. Polymorphisms of the VDR, which regulates bone metabolism-associated genes, have been reported in cases of aggressive and chronic periodontitis.

Principal findings: The translation initiation start codon polymorphism *VDR 27823*C/*C* genotype and the haplotype homozygote *ht1* (C–G–T) harbouring the *27823*C* allele were associated with an increased risk for GAP. The short VDR (*27823*C/*C*) protein may have a regulatory role in the development of GAP.

Practical implications: Short VDR (*27823*C/*C*) may constitute a candidate marker for GAP susceptibility.