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*Bsm*I, *Taq*I, *Apa*I, and *Fok*I polymorphisms in the vitamin D receptor gene and periodontitis: a meta-analysis of 15 studies including 1338 cases and 1302 controls

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Abstract

Aim: A meta-analysis was conducted in order to investigate the potential association of vitamin D receptor (VDR) gene polymorphisms with susceptibility to aggressive and chronic periodontal disease.

Material and Methods: A database search yielded a total of 15 studies involving 1338 cases and 1302 controls. Four polymorphisms were included in the meta-analysis: VDR *Taq*I (rs731236), VDR *Bsm*I (rs1544410), VDR *Fok*I (rs2228570), and VDR *Apa*I (rs7975232). Odds ratios (ORs) along with their 95% confidence intervals (CIs) were computed to compare the distribution of alleles and genotypes between cases and controls.

Results and Conclusions: The combined results based on all studies showed that (1) chronic periodontitis cases had a significantly lower frequency of bb genotype of *Bsm*I [OR = 0.63, 95% CI = 0.42, 0.94; $p = 0.02$] in Asians; (2) chronic periodontitis cases had a significantly higher frequency of AA genotype of *Apa*I (OR = 2.20, 95% CI = 1.39, 3.48; $p < 0.001$) in Asians; (3) chronic periodontitis cases had a weak significantly higher frequency of TT genotype of *Taq*I (OR = 1.86, 95% CI = 1.002, 3.46; $p = 0.049$) in Asians. After Bonferroni's correction, we found that in Asians chronic periodontitis cases still had a significantly higher frequency of AA genotype of *Apa*I. No significant difference was found in any genotype of *Fok*I. No association was found for all the VDR gene polymorphisms examined as far as the aggressive form of the disease is concerned. Future studies need to focus on the possible biological consequences and mechanisms of the VDR genetic variants. The current findings confirm that VDR gene is a candidate gene for periodontitis.

Key words: gene polymorphism; meta-analysis; periodontitis; Vitamin D receptor

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Conflict of interest and source of funding statement

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Periodontitis is an infection of the supporting tissues of the teeth. The periodontal disease emerges either with the chronic or the aggressive form (Armitage 1999), and affects a significant portion of the population (Albandar et al. 1999, Albandar et al. 2002). Chronic periodontitis is rather common affecting up to 30% of adults, while 7–13% of the adult population will develop severe forms of destructive periodontal disease (Nares 2003). Aggressive periodontitis, formerly described as early onset periodontitis, seems to be a less frequent occurring form of periodontitis (Papapanou 1999). Periodontitis is a chronic disease believed

to have a complex multifactorial aetiopathogenesis. Microbiological factors interact with genetic and environmental factors to determine disease onset and progression (Nibali et al. 2008).

Among putative genetic risk factors, a restriction fragment length polymorphism (RFLP) of the vitamin D receptor (VDR) gene has been associated previously with various infections and pathologies (Bellamy et al. 1999), including periodontitis, in different populations (Tachi et al. 2003, de Brito Junior et al. 2004, Brett et al. 2005, Park et al. 2006). Its mechanism of action is unclear and maybe a function of linkage disequilibrium (LD) with a functional polymorphism elsewhere in the VDR gene (Uitterlinden et al. 2004). A key feature of periodontal diseases is loss of alveolar bone. Many studies have identified potential gene polymorphisms that influence bone mineral density (BMD), turnover, and bone loss as they relate to osteoporosis. VDR gene polymorphisms have been strongly associated with BMD in some studies (Cooper & Umbach 1996, Gong et al. 1999, Thakkinstian et al. 2004, Uitterlinden et al. 2006). In the VDR gene, four common RFLPs (*Taq*I, *Bsm*I, *Fok*I, *Apa*I) have been associated with BMD.

Vitamin D influences the development of periodontal disease through both immunomodulatory effects and an effect on BMD (Krall et al. 2001). The VDR is involved in a variety of biologic processes, including bone metabolism, modulation of the immune response, and regulation of cell proliferation and differentiation (Uitterlinden et al. 2004). Many association studies have shown conflicting results of the relationship between VDR polymorphisms and susceptibility to aggressive and chronic periodontal disease (Yoshihara et al. 2001, Sun et al. 2002, Tachi et al. 2003, de Brito Junior et al. 2004, Zhang et al. 2005, Park et al. 2006, de Souza et al. 2007, Naito et al. 2007, Gunes et al. 2008, Li et al. 2008, Nibali et al. 2008, Wang et al. 2008, Borges et al. 2009, Wang et al. 2009, Zhang et al. 2010). Therefore, we decided to perform a meta-analysis to study whether a relationship exists between *Taq*I, *Bsm*I, *Fok*I, and *Apa*I polymorphisms in the VDR gene and susceptibility to aggressive and chronic periodontal disease.

Material and Methods

Search strategy

A comprehensive search of Medline (1966–June 2010), Embase (January 1966–June 2010), and Current Contents (1998–June 2010) was conducted to identify published epidemiologic studies related to polymorphisms of VDR gene and periodontitis. The medical subject headings ''VDR,'' ''genetic polymorphism,'' ''periodontitis,'' ''periodontal disease,'' and the free-text words ''VDR'' were combined. No language or other restrictions were placed on the search. Furthermore, references cited in published original and review articles were examined until no further study was identified. Authors of retrieved articles were contacted where necessary and were asked to provide additional information. The search was expanded by reviewing special meeting issues of journals in order to retrieve abstracts not included in computer indices.

Inclusion and exclusion criteria

Articles from peer-reviewed medical journals were included if they reported on studies using a case–control, cohort, nested case–control, or cross-sectional design and provided sufficient data to calculate an odds ratio (OR) and corresponding 95% confidence interval (CI). Four polymorphisms were included in the meta-analysis: VDR *Taq*I (rs731236), VDR *Bsm*I (rs1544410), VDR *Fok*I (rs2228570), and VDR *Apa*I (rs7975232). Interim analyses, overlapping study populations, animal study, and comparisons of laboratory methods were excluded. To avoid selection bias, published manuscripts were considered for review without any language or quality restrictions.

Data extraction

Study characteristics extracted from each paper included country, year of publication, design, race, study period, genotyping method, form of disease, number of cases, and controls. Data were extracted by two of the authors from each article using a structured sheet and they entered them into a database. Any disagreement between researchers was resolved by continuing discussions until a consensus was reached.

Statistical analysis

We tested the heterogeneity of the included studies with Q statistics, $p<0.1$ was considered statistically significant. Heterogeneity was also assessed through visual examination of L'Abbe plots (Song 1999). The Mantel–Haenszel method for fixed effects and the Der–Simonian–Laird method for random effects were used to estimate pooled OR (Robins et al. 1986). We used fixed-effects methods if the result of the Q test was not significant. Otherwise, we calculated pooled estimates and CIs assuming a random-effects model. Data are shown as OR with 95% CI, with two-tailed p-values and statistical significance was set at $p<0.05$ (two-tailed). Because the SNPs rs731236, rs7975232, and rs1544410 are located very close on the chromosomal map and are in very tight LD in the HapMap JPT+CHB and the HapMap CEU populations, these SNPs could be regarded as not independent tests, which would reduce the necessary Bonferroni's correction to the factor 2.

Publication bias was investigated both visually by using a funnel plot and statistically via Begg funnel plots and the Egger's bias test, which measures the degree of funnel plot asymmetry (Begg & Mazumdar 1994, Egger et al. 1997). The statistical analysis was conducted using STATA 8.0 (StataCorp, College Station, Tx, USA).

Results

Eligible studies

There were 76 papers relevant to the searching words (Fig. 1). Through the step of screening the title, 41 of these articles were excluded (29 were not polymorphisms, 8 were not case–control studies, 4 were not conducted in humans). Abstracts from 35 articles were reviewed and an additional 17 trials were excluded (14 were not case–control studies, 3 were not conducted in humans), leaving 18 studies for full publication review. Of these, 3 were excluded (2 were not case–control studies [Inagaki et al. 2003, Tian et al. 2010), 1 was for localized early-onset periodontal diseases (Hennig et al. 1999)]. After a careful screening of the published literature, our meta-analysis identified 15 published studies involving 1338 cases and 1302 controls (Yoshihara et al. 2001, Sun et al. 2002, Tachi et al. 2003, de Brito Junior et al. 2004, Zhang et al. 2005, Park et al. 2006, de Souza et al. 2007, Naito et al. 2007, Gunes et al. 2008, Li et al. 2008, Nibali et al. 2008, Wang et al. 2008, Borges et al. 2009, Wang et al. 2009, Zhang et al. 2010). Ten studies reported on Asians, and five studies reported on Caucasians.

Of these studies, 11 reported chronic periodontitis, and six reported aggressive periodontitis. All of these studies were hospital-based case–control studies. There were 12 comparisons for *Taq*I polymorphism, 10 comparisons for *Bsm*I polymorphism, five comparisons for *Fok*I polymorphism, and five comparisons for *Apa*I polymorphism. Studies were conducted in United Kingdom, Brazil, Turkey, Japan, Korea, and China. Characteristics of studies included in this meta-analysis are presented in Table 1.

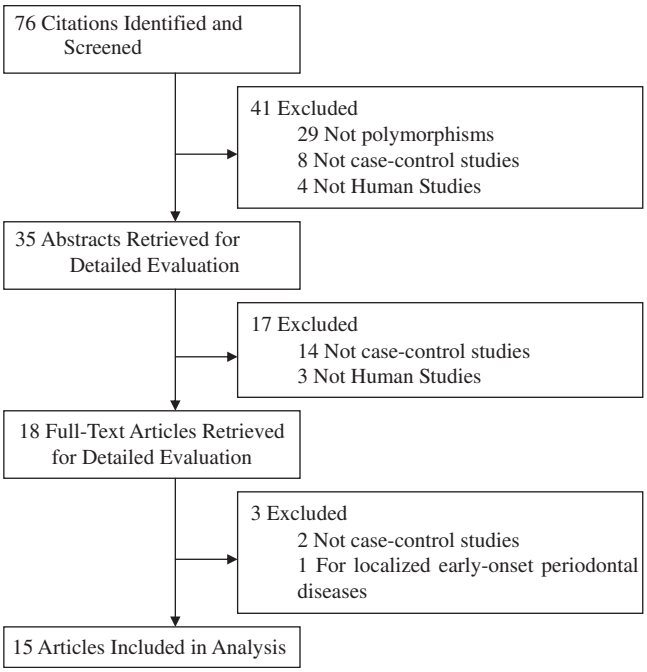

Fig. 1. Studies identification, inclusion, and exclusion.

Quantitative data synthesis

The combined results based on all studies showed that (1) chronic periodontitis cases had a significantly lower frequency of bb genotype of *Bsm*I [OR = 0.63, 95% CI = 0.42, 0.94; $p = 0.02$] in Asians (Table 2, Fig. 2); (2) chronic periodontitis cases had a significantly higher frequency of AA genotype of *Apa*I (OR = 2.20, 95% CI = 1.39, 3.48; $p < 0.001$) in Asians (Table 2, Fig. 3); and (3) chronic periodontitis cases had a weak significantly higher frequency of TT genotype of *Taq*I (OR = 1.86, 95% CI = 1.002, 3.46; $p = 0.049$) in Asians (Table 2, Fig. 4). After Bonferroni's correction, we found that in Asians chronic periodontitis cases still had a significantly higher frequency of AA genotype of *ApaI*. No significant difference was found in any genotype of *Fok*I (Table 2). No association was found for all the VDR gene polymorphisms examined as far as the aggressive form of the disease is concerned (Table 3). Genotype counts of the analysed polymorphisms of studies included in the meta-analysis are presented in Table 4.

Publication bias and heterogeneity

We selected *Taq*I polymorphisms to investigate the publication bias. No evidence of publication bias was found by the Begg rank correlation method ($p = 1.00$) and the Egger weighted regression method ($p = 0.96$) (Figs 5 and 6). Heterogeneity of included studies of each polymorphism is presented in Table 2 and Table 3.

Discussion

The current meta-analysis of 15 studies is the first quantitative evaluation of the potential association of VDR gene polymorphisms with susceptibility to aggressive and chronic periodontal disease. We found that chronic periodontitis cases had a significantly lower frequency of bb genotype of *Bsm*I, higher frequency of AA genotype of *Apa*I, and

Table 1. Characteristics of studies included in the meta-analysis

Study	Design	Country	Genotyping method	Cases	Controls	Form of disease	Polymorphisms	HWE*
Zhang et al. (2010)	HCC	China	PCR-RFLP	124	91	Aggressive, chronic	*Taq*I	0.7
Wang et al. (2009)	HCC	China	PCR-RFLP	107	121	Chronic	*Taq*I, *Bsm*I, *Fok*I, *Apa*I	0.6
Borges et al. (2009)	HCC	Brazil	PCR-RFLP	30	30	Chronic	*Taq*I	0.09
Wang et al. (2008)	HCC	China	PCR-RFLP	106	80	Chronic	*Bsm*I	<0.001
Nibali et al. (2008)	HCC	UK	PCR-RFLP	303	231	Aggressive, chronic	*Taq*I	0.24
Li et al. (2008)	HCC	China	PCR-RFLP	51	53	Aggressive	*Taq*I, *Bsm*I, *Fok*I, *Apa*I	0.78
Gunes et al. (2008)	HCC	Turkey	PCR-RFLP	72	102	Chronic	*Taq*I, *Bsm*I, *Apa*I	0.24
Naito et al. (2007)	HCC	Japan	PCR	17	80	Chronic	*Bsm*I, *Fok*I, *Apa*I	0.35
de Souza et al. (2007)	HCC	Brazil	PCR-RFLP	50	59	Chronic	*Taq*I, *Bsm*I	0.06
Park et al. (2006)	HCC	Korea	PCR-RFLP	93	143	Aggressive	*Taq*I, *Bsm*I, *Fok*I	0.70
Zhang et al. (2005)	HCC	China	PCR-RFLP	166	80	Chronic	*Taq*I, *Bsm*I, *Apa*I	0.12
de Brito Junior et al. (2004)	HCC	Brazil	PCR	69	44	Chronic	*Bsm*I, *Taq*I	0.36
Tachi et al. (2003)	HCC	Japan	PCR-RFLP	74	94	Chronic	*Taq*I, *Fok*I	0.20
Sun et al. (2002)	HCC	China	PCR	24	39	Aggressive	*Taq*I	0.87
Yoshihara et al. (2001)	HCC	Japan	PCR-RFLP	52	55	Aggressive	*Bsm*I	0.41

HCC, hospital-based case–control; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; HWE, Hardy–Weinberg equilibrium.
*p-value for controls.

Table 2. Meta-analysis of polymorphisms of VDR gene and chronic periodontitis

VDR polymorphisms/ race/country	No. of studies	OR (95% CI) XX	*p* of OR	*p* of heterogeneity	OR (95% CI) Xx	*p* of OR	*p* of heterogeneity	OR (95% CI) xx	*p* of OR	*p* of heterogeneity
*Taq*I (rs731236)										
Asians	4	1.86 (1.002, 3.46)	0.049	0.21	0.51 (0.26, 1.01)	0.05	0.16	3.42 (0.14, 84.91)	0.45	NA
China	3	1.67 (0.69, 4.00)	0.25	0.15	0.56 (0.21, 1.50)	0.25	0.10	3.42 (0.14, 84.91)	0.45	NA
Japan	1	2.52 (1.05, 6.05)	0.04	NA	0.40 (0.17, 0.95)	0.04	NA	NA	NA	NA
Caucasians	5	0.78 (0.45, 1.37)	0.40	0.02	1.36 (0.74, 2.49)	0.32	0.01	0.83 (0.51, 1.34)	0.44	0.49
Brazil	3	0.52 (0.24, 1.13)	0.10	0.09	2.10 (0.89, 4.96)	0.09	0.05	0.80 (0.39, 1.64)	0.54	0.66
Turkey	1	1.13 (0.62, 2.06)	0.70	NA	0.74 (0.40, 1.37)	0.35	NA	1.70 (0.59, 4.91)	0.33	NA
UK	1	1.43 (0.77, 2.65)	0.26	NA	0.86 (0.46, 1.60)	0.64	NA	0.55 (0.23, 1.34)	0.19	NA
*Bsm*I (rs1544410)										
Asians	4	1.68 (0.93, 3.06)	0.09	0.37	1.39 (0.87, 2.24)	0.17	0.91	0.63 (0.42, 0.94)	0.02	0.96
China	3	1.68 (0.93, 3.06)	0.09	0.37	1.40 (0.84, 2.34)	0.20	0.77	0.62 (0.41, 0.94)	0.03	0.90
Japan	1	NA	NA	NA	1.33 (0.38, 4.67)	0.65	NA	0.75 (0.21, 2.63)	0.65	NA
Caucasians	3	0.85 (0.49, 1.49)	0.58	0.20	1.27 (0.85, 1.90)	0.24	0.12	0.84 (0.56, 1.27)	0.42	0.17
Brazil	2	0.60 (0.29, 1.20)	0.15	0.52	1.77 (1.03, 3.05)	0.04	0.29	0.76 (0.43, 1.32)	0.32	0.07
Turkey	1	1.67 (0.64, 4.34)	0.30	NA	0.85 (0.46, 1.55)	0.59	NA	0.96 (0.52, 1.78)	0.91	NA
*Fok*I (rs2228570)										
Asians	3	0.72 (0.46, 1.14)	0.16	0.54	1.18 (0.81, 1.71)	0.38	0.06	1.07 (0.71, 1.62)	0.75	0.23
China	1	0.58 (0.26, 1.27)	0.17	NA	1.48 (0.88, 2.52)	0.14	NA	0.87 (0.52, 1.47)	0.61	NA
Japan	2	0.81 (0.46, 1.42)	0.46	0.39	0.94 (0.55, 1.59)	0.82	0.03	1.50 (0.77, 2.92)	0.23	0.24
Caucasians	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
*Apa*I (rs7975232)										
Asians	3	2.20 (1.39, 3.48)	0.001	<0.001	1.19(0.83, 1.70)	0.33	0.09	0.52 (0.16, 1.70)	0.28	0.001
China	2	2.11 (1.28, 3.50)	0.004	<0.001	1.38(0.94, 2.01)	0.10	0.69	0.42 (0.10, 1.79)	0.24	<0.001
Japan	1	2.65 (0.86, 8.23)	0.09	NA	0.31(0.08, 1.15)	0.08	NA	1.05 (0.21, 5.37)	0.95	NA
Caucasians	1	1.31 (0.71, 2.42)	0.38	NA	0.64(0.34, 1.21)	0.17	NA	1.25 (0.59, 2.63)	0.56	NA
Turkey	1	1.31 (0.71, 2.42)	0.38	NA	0.64(0.34, 1.21)	0.17	NA	1.25 (0.59, 2.63)	0.56	NA

VDR, vitamin D receptor; OR, odds ratio; CI, confidence interval; X/x for B/b of *Bsm*I, A/a of *Apa*I, T/t of *Taq*I, F/f of *Fok*I; NA, not applicable.

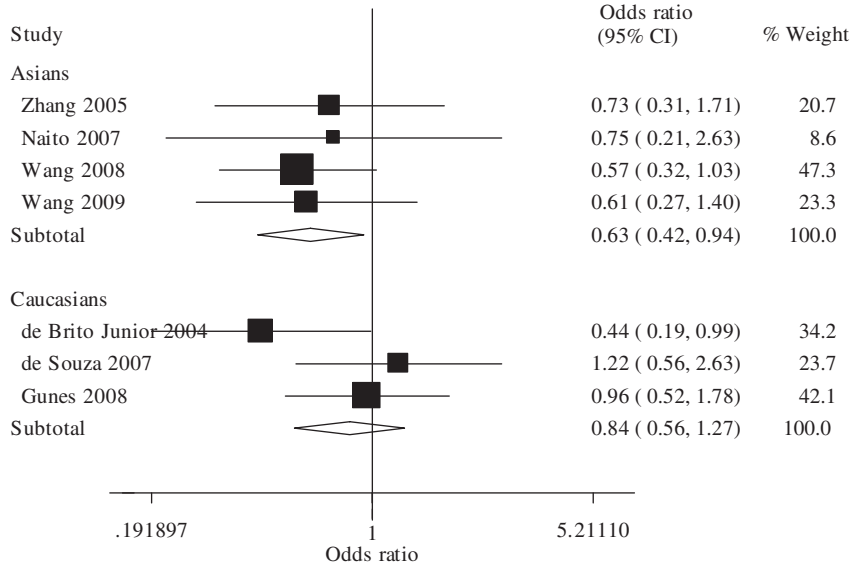

Fig. 2. Meta-analysis of *Bsm*I bb and chronic periodontitis.

TT genotype of *Taq*I in Asians. After Bonferroni's correction, we found that in Asians chronic periodontitis cases still had a significantly higher frequency of AA genotype of *ApaI*. No significant difference was found in any genotype of *Fok*I. No association was found for all the VDR gene polymorphisms examined as far as the aggressive form of the disease is concerned.

Although numerous association studies relating polymorphisms in this gene to periodontitis have been published, results are conflicting, possibly because of variations in study design, small sample sizes, and heterogeneous populations, among other issues. Meta-analysis may be able to overcome the shortcomings of individual studies; by systematically combining results from individual studies, this method increases the power to detect an association, increases the precision of the magnitude of effect, and sheds light on reasons for discrepant results by exploring heterogeneity (Ioannidis et al. 2001).

The mechanism by which VDR gene polymorphisms influence the incidence of periodontitis has not been clarified. Accumulating evidence from basic and clinical research makes the association between the VDR gene polymorphism and periodontal disease biologically plausible. VDR gene polymorphisms have been strongly associated with BMD in many studies since 1994 (Melhus et al. 1994, Morrison et al. 1994, Yamagata et al. 1994). There have been four meta-analyses to summarize association studies between VDR polymorphisms and BMD (Cooper & Umbach 1996, Gong et al. 1999, Thakkinstian et al. 2004, Uitterlinden et al. 2006). Some investigators presumed that the VDR polymorphisms influence bone resorption and immune function (Mathieu et al. 2001, Froicu & Cantorna 2007, van Etten et al. 2007, Garcia et al.

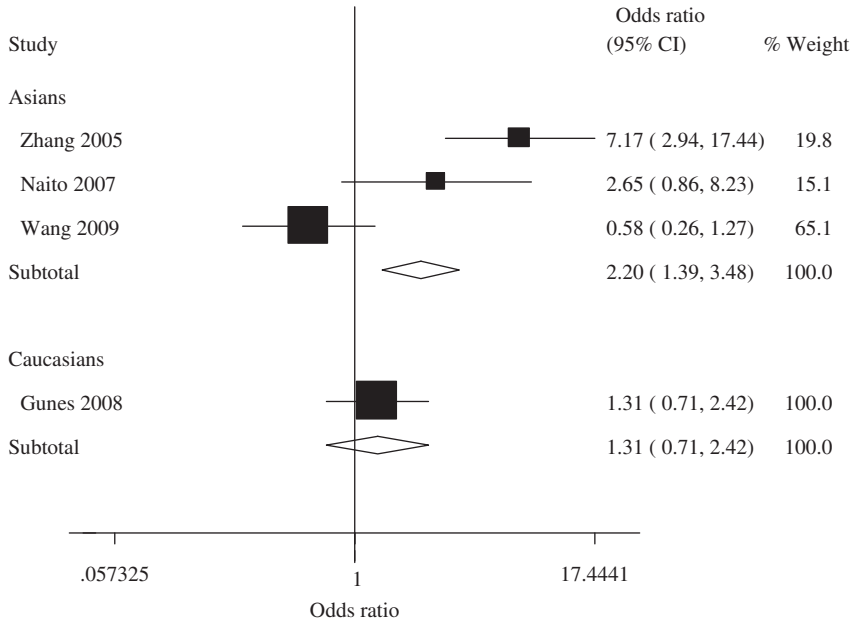

Fig. 3. Meta-analysis of *Apa*I AA and chronic periodontitis.

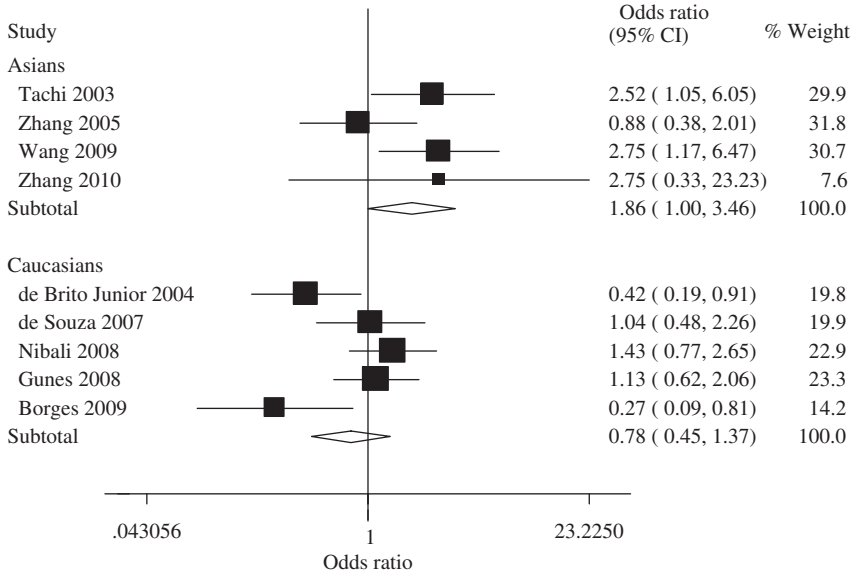

Fig. 4. Meta-analysis of *Taq*I TT and chronic periodontitis.

2007). Several studies on the association between VDR polymorphisms and autoimmune diseases have been reported (Fan et al. 2005, Kanazawa et al. 2006, Birlea et al. 2006, Maalej et al. 2008). In the current study, we found that chronic periodontitis cases had a significantly lower frequency of bb genotype of *Bsm*I, higher frequency of AA genotype of *Apa*I and TT genotype of *Taq*I in Asians.

Hardy–Weinberg equilibrium (HWE) for all studies had been calculated (Table 1). A departure from HWE can also imply possible ethnic admixture in the population, if the polymorphic site varies in genotype by race. In fact, race-specific variation in the distribution of genotypes in the VDR gene polymorphism has been demonstrated. Because race may be related to disease, either through common risk factors or other genes in LD with VDR gene, confounding by race, or population stratification, may have biased results in studies conducted on ethnically diverse populations that did not account for possible confounding. Ingles et al. (1997) demonstrated that the strength of the LD varied by ethnicity, with departures from complete disequilibrium producing disagreement between the *Bsm*I and poly(A) genotypes. Genotypic a disagreement was lowest in Japanese-Americans and non-Hispanic whites (6% and 7%, respectively), intermediate in Chinese and Hispanics (11% and 19%, respectively), and the highest among African-Americans (37%) (Ingles et al. 1997).

Although we have investigated the four SNPs in four independent hypotheses, the SNPs rs731236, rs7975232, and rs1544410 are located very close on the chromosomal map and are in very tight LD in the HapMap JPT+CHB and the HapMap CEU populations. Thus, they can be regarded as reflecting one haplotype block of high LD if the LD was $r^2 < 0.8$. This could reduce the correction for multiple testing to the factor of 2. In this case, after Bonferroni's correction, we found that in Asians chronic periodontitis cases still had a significantly higher frequency of AA genotype of *Apa*I.

With this meta-analysis, we present for the first time evidence that at least in Asians chronic periodontitis cases had a significantly lower frequency of bb genotype of *Bsm*I, higher frequency of AA genotype of *Apa*I and TT genotype of *Taq*I. No significant difference was found in any genotype of *Fok*I. If the observed associations were true, they likely reflect a single causative variant, which has not been identified yet, but is tagged by the three associated SNPs. No associations were observed for the non-Asian populations. This may be due to a lack of statistical power, population stratification between distantly related Caucasian populations or a lack of this association in Caucasians. In this meta-analysis, we found no association with AgP in the Asian and the Caucasian populations. However, AgP is generally considered as the disease phenotype with a much higher genetic predisposition than CP. This may be due to different disease mechanisms of both sub-phenotypes or a lack of statistical power in the AgP populations. Another reason for such a discrepancy include the frequency of the polymorphism in the population studied or LD with other, perhaps undiscovered, functional SNPs in the VDR gene.

Periodontitis is a chronic disease believed to have a complex multifactorial aetiopathogenesis. Microbiological factors interact with genetic and environmental factors to determine disease onset and progression. Future studies should carefully address such interactions, i.e. performing stratified analyses

Table 3. Meta-analysis of polymorphisms of VDR gene and aggressive periodontitis

VDR polymorphisms/ race	No. of studies	OR (95% CI) XX	*p* of OR	*p* of heterogeneity	OR (95% CI) Xx	*p* of OR	*p* of heterogeneity	OR (95% CI) xx	*p* of OR	*p* of heterogeneity
*Taq*I (rs731236)										
Asians	4	0.73 (0.41, 1.28)	0.27	0.51	1.37 (0.78, 2.41)	0.27	0.51	NA	NA	NA
China	3	0.65 (0.33, 1.30)	0.22	0.37	1.53 (0.77, 3.04)	0.22	0.37	NA	NA	NA
Korea	1	0.92 (0.34, 2.52)	0.88	NA	1.08 (0.40, 2.95)	0.88	NA	NA	NA	NA
Caucasians	1	1.06 (0.64, 1.77)	0.82	NA	1.14 (0.69, 1.87)	0.61	NA	0.57 (0.28, 1.15)	0.12	NA
UK	1	1.06 (0.64, 1.77)	0.82	NA	1.14 (0.69, 1.87)	0.61	NA	0.57 (0.28, 1.15)	0.12	NA
*Bsm*I (rs1544410)										
Asians	3	NA	NA	NA	1.00 (0.52, 1.89)	0.99	0.93	1.00 (0.53, 1.90)	0.99	0.93
China	1	NA	NA	NA	0.77 (0.16, 3.60)	0.74	NA	1.31 (0.28, 6.15)	0.74	NA
Korea	1	NA	NA	NA	1.07 (0.42, 2.74)	0.88	NA	0.93 (0.36, 2.38)	0.88	NA
Japan	1	NA	NA	NA	1.03 (0.35, 2.99)	0.96	NA	0.97 (0.33, 2.83)	0.96	NA
Caucasians	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
*Fok*I (rs2228570)										
Asians	2	1.51 (0.45, 5.09)	0.51	0.04	0.67 (0.44, 1.04)	0.08	0.63	0.96 (0.25, 3.76)	0.95	0.01
China	1	2.90 (1.16, 7.24)	0.02	NA	0.79 (0.37, 1.71)	0.55	NA	0.45 (0.18, 1.14)	0.09	NA
Korea	1	0.84 (0.41, 1.71)	0.62	NA	0.63 (0.37, 1.06)	0.08	NA	1.83 (1.06, 3.16)	0.03	NA
Caucasians	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
*Apa*I (rs7975232)										
Asians	1	0.96 (0.42, 2.23)	0.93	NA	0.80 (0.37, 1.72)	0.56	NA	1.55 (0.57, 4.23)	0.40	NA
China	1	0.96 (0.42, 2.23)	0.93	NA	0.80 (0.37, 1.72)	0.56	NA	1.55 (0.57, 4.23)	0.40	NA
Caucasians	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

VDR, vitamin D receptor; OR, odds ratio; CI, confidence interval; X/x for B/b of *Bsm*I, A/a of *Apa*I, T/t of *Taq*I, F/f of *Fok*I; NA, not applicable.

Table 4. Genotype counts of the analyzed polymorphisms of studies included in the meta-analysis

Study	AgP	CP	Controls	Form of disease	Polymorphisms	XX (case)	Xx (case)	xx (case)	X (%) (case)	XX (control)	Xx (control)	xx (control)	X (%) (control)
Zhang et al. (2010)	90	34	91	Aggressive	*Taq*I	75	15	0	165 (91.7)	84	7	0	175 (96.2)
				Chronic	*Taq*I	33	1	0	67 (98.5)	84	7	0	175 (96.2)
Wang et al. (2009)	DNR	107	121	Chronic	*Taq*I	99	7	1	205 (95.8)	99	22	0	220 (90.9)
					*Bsm*I	0	15	92	15 (7.0)	0	11	110	11 (4.5)
					*Fok*I	29	62	16	120 (56.1)	37	65	19	139 (57.4)
					*Apa*I	11	51	45	73 (34.1)	20	46	55	86 (35.5)
Borges et al. (2009)	DNR	30	30	Chronic	*Taq*I	7	18	5	32 (53.3)	16	9	5	41 (68.3)
Wang et al. (2008)	DNR	106	80	Chronic	*Bsm*I	46	11	49	103 (48.6)	24	8	48	56 (35.0)
Nibali et al. (2008)	224	79	231	Aggressive	*Taq*I	44	54	14	142 (31.7)	53	63	28	169 (58.7)
				Chronic	*Taq*I	27	24	7	78 (49.4)	53	63	28	169 (58.7)
Li et al. (2008)	51	DNR	53	Aggressive	*Taq*I	45	6	0	96 (94.1)	46	7	0	99 (93.4)
					*Bsm*I	0	3	48	3 (2.9)	0	4	49	4 (3.8)
					*Fok*I	19	23	9	61 (59.8)	9	27	17	45 (42.5)
					*Apa*I	15	25	11	55 (53.9)	16	29	8	61 (57.5)
Gunes et al. (2008)	DNR	72	102	Chronic	*Taq*I	36	28	8	100 (69.4)	48	47	7	143 (70.1)
					*Bsm*I	10	33	29	53 (36.8)	9	51	42	69 (33.8)
					*Apa*I	33	23	16	89 (61.8)	40	43	19	123 (60.3)
Naito et al. (2007)	DNR	17	80	Chronic	*Bsm*I	0	4	13	4 (11.8)	0	15	65	15 (9.4)
					*Fok*I	4	4	9	12 (35.3)	15	40	25	70 (43.8)
					*Apa*I	12	3	2	27 (79.4)	38	33	9	109 (68.1)
de Souza et al. (2007)	DNR	50	59	Chronic	*Taq*I	20	24	6	64 (64.0)	23	29	7	75 (63.6)
					*Bsm*I	7	22	21	36 (36.0)	15	22	22	52 (44.1)
Park et al. (2006)	93	DNR	143	Aggressive	*Taq*I	86	7	0	179 (96.2)	133	10	0	276 (96.5)
					*Bsm*I	0	6	87	6 (3.2)	0	9	134	9 (3.1)
					*Fok*I	14	38	41	66 (35.5)	25	75	43	125 (43.7)
Zhang et al. (2005)	DNR	166	80	Chronic	*Taq*I	145	21	0	311 (93.7)	71	9	0	151 (94.4)
					*Bsm*I	1	21	144	23 (6.9)	1	7	72	9 (5.6)
					*Apa*I	61	74	31	196 (59.0)	6	31	43	43 (26.9)
de Brito Junior et al. (2004)	DNR	69	44	Chronic	*Taq*I	23	41	5	87 (63.0)	24	14	6	62 (70.5)
					*Bsm*I	10	43	16	63 (45.7)	8	18	18	34 (38.6)
Tachi et al. (2003)	DNR	74	94	Chronic	*Taq*I	66	8	0	140 (94.6)	72	22	0	166 (88.3)
					*Fok*I	28	35	11	91 (61.5)	43	38	13	124 (66.0)
Sun et al. (2002)	24	DNR	39	Aggressive	*Taq*I	23	1	0	47 (97.9)	37	2	0	76 (97.4)
Yoshihara et al. (2001)	52	DNR	55	Aggressive	*Bsm*I	0	11	41	11 (10.6)	0	11	44	11 (10.0)

AgP, aggressive periodontitis; CR, chronic periodontitis; DNR, data not report; X/x for B/b of *Bsm*I, A/a of *Apa*I, T/t of *Taq*I, F/f of *Fok*I.

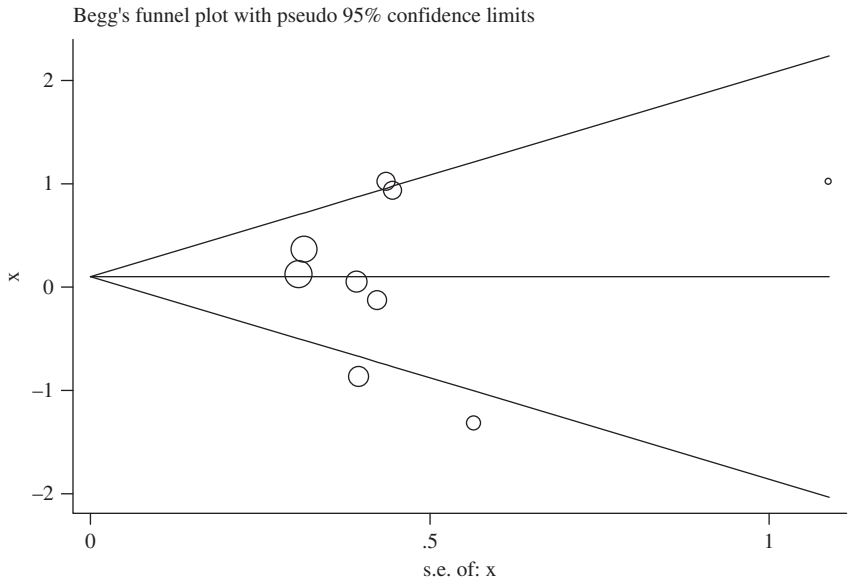

Fig. 5. Begg's funnel plot of *Taq*I and chronic periodontitis.

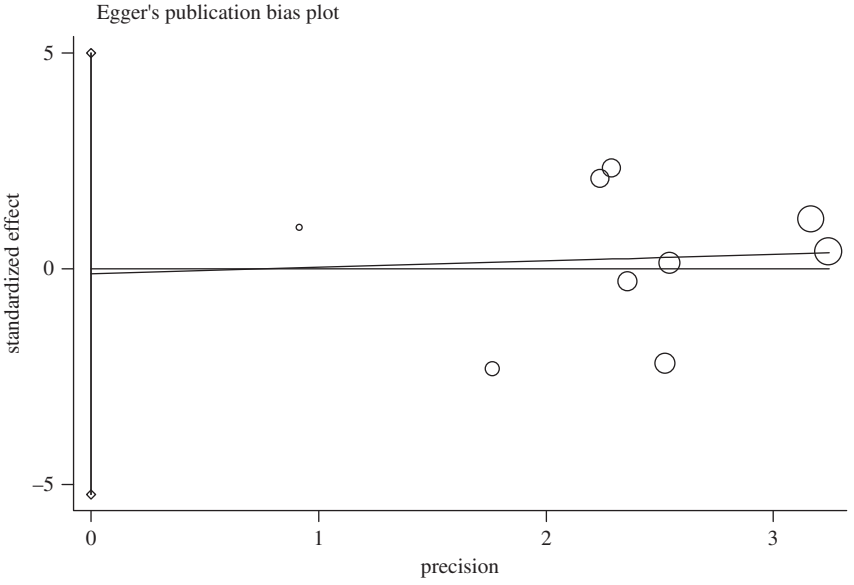

Fig. 6. Egger's publication bias plot of *Taq*I and chronic periodontitis.

that could be used in a subsequent meta-analysis (Nikolopoulos et al. 2008). On the other hand, the list of candidate susceptibility loci is continuously expanding but most of the reported associations are not replicated in subsequent research (Loos et al. 2005, Nikolopoulos et al. 2008). Even if genetic effects are repeatedly observed, their small impact may not result in routine screening recommendations and clinical benefits in the near future. However, the knowledge of the genetic determinants helps to understand better and deeply the causal pathways of a multifactorial disease such as periodontitis. One other suggestion for future research, thus, concerns the conduction of studies that address simultaneously the combined effect of two or more single nucleotide gene polymorphisms perhaps by haplotype analysis (Nikolopoulos et al. 2008). We found that chronic periodontitis cases had a significantly lower frequency of bb genotype of *Bsm*I, higher frequency of AA genotype of *Apa*I and TT genotype of *Taq*I in Asians.

Some meta-analyses have studied the relationship between VDR gene polymorphisms and other disease. The meta-analysis by Gao et al. (2010) found that VDR genetic polymorphisms were significantly associated with the development of tuberculosis. The meta-analysis by Zhou et al. (2009) suggested that *Apa*I, *Bsm*I, and *Fok*I polymorphisms in the VDR gene were associated with susceptibility to Graves' disease in Asian populations. The meta-analysis by Yin et al. (2009) suggested that the *Taq*I t and *Bsm*I B alleles were associated with a reduced prostate cancer risk among all study populations. The meta-analysis by Tang et al. (2009) showed that *Fok*I might be a susceptibility biomarker for breast cancer especially in European population. The meta-analysis by Raimondi et al. (2009) showed that VDR *Fok*I and *Bsm*I polymorphisms might modulate the risk of cancer of breast, skin, and prostate and possibly affect cancer risk at any site in Caucasians.

Some shortcomings of the analysis should be discussed. Firstly, the results were based on unadjusted estimates. A more precise analysis should be conducted with individual data. Periodontitis is a complex disease, and modifying factors such as smoking might possibly have an effect on genetic associations with periodontitis phenotypes. However, we were not capable of conducting genotype-stratified analyses due to the lack of properly reported sufficient data from the primary studies. Secondly, meta-analysis remains retrospective research that is subject to the methodological deficiencies of the included studies. Sources of bias are not controlled by the method. As we all know, a good meta-analysis of badly designed studies will still result in bad statistics. Thirdly, our meta-analysis combined the genetic association studies performed from 2001 with the more current ones, most of these studies performed before ''Strengthening the reporting of genetic association studies (STREGA): an extension of the STROBE Statement'', which was published in Hum Genet (Little et al. 2009). Actually, all the issues are important to be considered in genetic association studies. But we often could not find these issues in some of the studies included in our meta-analysis. Fourthly, the statistical synthesis of gene–disease association studies in the field of periodontology pertains to many biases because of the small number of subjects enrolled in individual studies, the heterogeneity in periodontitis definition, the performance of multiple tests, and the inappropriate selection of controls (Dimou et al. 2010). Although no evidence of publication bias was found by

the Begg rank correlation method and the Egger weighted regression method, we invested a great deal of efforts in limiting possible source of bias by avoiding any form of quality scoring, searching for reports not included in electronic databases, retrieving eligible non-English articles, assessing the effect of HWE violations, applying multivariate meta-analytic techniques, performing statistical tests for detecting publication bias, and evaluating the existence of a time trend in the summary estimates (Dimou et al. 2010). Finally, The Caucasian populations in the meta-analyses are very diverse and cannot be regarded as a homogenous ethnicity (e.g. the Brazilian population consists of white Europeans, Hispanics, Africans, the UK analysis population might consist to some extent of Pakistani, Indians, and North-West Europeans, and the Turkish differ very much from the North-West Europeans in respect of genetic population structure). This might have stratified the analysis, possibly leading to the negative results. On the other hand, the allele frequencies of the analysed SNPs are different between Asians and Caucasians. This might reflect the different LD structure at this genetic locus, and it is possible that the three neighbouring SNPs do not tag the causative variant.

In conclusion, this meta-analysis suggested that chronic periodontitis cases had a significantly lower frequency of bb genotype of *Bsm*I, higher frequency of AA genotype of *Apa*I and TT genotype of *Taq*I in Asians. After the Bonferroni correction, we found that in Asians chronic periodontitis cases still had a significantly higher frequency of AA genotype of *Apa*I. However, currently we have no indication as to the meaning and biological events related to this finding; functional studies and the role of the VDR need further research in the field of periodontology.

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Clinical Relevance

Scientific rationale for the study: Conflicting results have been presented in the past concerning genetic variants in the VDR gene in relation to the susceptibility to periodontitis.

Principal findings: With this meta-analysis, we present for the first time evidence that at least in Asians chronic periodontitis cases had a significantly higher frequency of AA genotype of *Apa*I.

Practical implications: At this point, however, the finding has no practical implications yet. First, biological consequences and mechanisms need further research.