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Meta-Analysis

Association between vitamin D receptor BsmI gene polymorphism and periodontitis: a meta-analysis in a single ethnic group

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Abstract: Although many researchers have studied on the association between vitamin D receptor (VDR) BsmI polymorphism and periodontitis, this association remains elusive. To further assess the effects of VDR BsmI polymorphism on the risk of periodontitis, a meta-analysis was performed in a single ethnic group. We searched PubMed and Chinese databases for relevant studies till April 2017. The strength of the associations were assessed used pooled odds ratios (ORs) and 95% confidence intervals (CIs). Six studies including 757 periodontitis cases and 670 controls were identified at last. In the total analyses, VDR BsmI polymorphism was not associated with the risk of periodontitis in all models. The subgroup analyses suggested a significantly reduced risk of periodontitis in South China. In conclusion, our meta-analysis showed that VDR BsmI polymorphism was associated with the decreased risk of periodontitis in Chinese individuals from South China, and further studies in other ethic groups are required for definite conclusions.

Key words: Meta-analysis; Vitamin D receptor; Polymorphism; Periodontitis.

Introduction

Periodontitis is one of the widespread and complex inflammatory diseases in human and with high prevalence of 10–15% (1). It major consisted of chronic periodontitis (CP) and aggressive periodontitis (AP) (2). A growing body of evidence indicates that genetic and environmental risk factors may induce periodontitis (3). In recent years, many candidate genes have been identified as potential periodontitis susceptibility loci. An important gene among these is vitamin D receptor (VDR), which is is located on chromosome 1p12. It is clear that mutations in functionally critical areas of VDR gene can have profound effects on mineral metabolism and bone mineral density (4,5). Several VDR gene polymorphisms have been identified; of these the BsmI single nucleotide polymorphism has been extensively studied. In 2001, a first study on the association between VDR BsmI polymorphism and generalized early-onset periodontitis in Japanese patients (6). As a consequence, many studies have attempted to clarify this relationship, but there has been no definite consensus to date. Differences in results may be related to the ethnic and clinical heterogeneity of the patients studied or to the relatively small numbers of patients in each study. Meta-analysis is one way to overcome the problems of small sample size and and inadequate statistical power. For addressing the association between VDR BsmI polymorphism and periodontitis risk better, we performed a meta-analysis in a single ethnic group to lessen the impact of different genetic background.

Materials and Methods

Search strategy and selection criteria

We performed a search for studies that examined associations between VDR BsmI polymorphism and periodontitis before April 2017. The literature was searched using the PubMed and Chinese databases to identify available articles in which VDR BsmI polymorphism was analyzed in periodontitis patients. The search keywords were used: (periodontitis or periodontal disease) and (vitamin D receptor or VDR) and (China or Chinese or Taiwan). References in identified studies were also investigated to identify additional studies not indexed by the electronic databases. No language restriction was applied.

Inclusion criteria: (1) they were case-control or cohort studies describing the association of the VDR BsmI polymorphism and periodontitis, (2) they provided the genetypes in cases and controls, (3) participants were Chinese population. Exclusion criteria: (1) repeated literatures, (2) incomplete data, (3) case-only articles, (4) review articles and abstracts, (5) participants with systematic diseases.

Data extraction

We conducted a systematic review and meta-analysis in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Data were extracted from all eligible publications by two independent reviewers. Discrepancy between the reviewers was resolved by a discussion between the two reviewers. Data

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

References	Type of periodontitis	Source of controls	Geographic area(s)	Case number	Control number	Cases			Controls			HWE	
						BB	Bb	bb	BB	Bb	bb	χ^2	*P*
Zhang 2005	CP	HB	Sichuan	166	80	1	21	144	1	7	72	2.47	0.116
Wang 2008	CP	PB	Liaoning	106	80	46	11	49	24	8	48	48.70	0.000
Li 2008	AP	PB	Jiangsu	51	53	0	3	48	0	4	49	0.08	0.775
Wang 2009	CP	PB	Guangdong	107	121	0	15	92	0	11	110	0.27	0.600
Shao 2013	CP	PB	Yunnan	232	246	43	7	182	33	1	212	237.57	0.000
Wu 2015	CP	PB	Xinjiang	95	90	12	25	58	19	35	36	3.37	0.066

PB: population-based; HB: hospital-based.

extracted from identified studies included first author's name, publication year, type of periodontitis, source of controls, geographic area(s), sample size, and number of subjects with VDR BsmI genotypes.

Statistical analysis

We performed meta-analyses using: (1) allelic contrast, (2) contrast of homozygotes, (3) recessive, and (4) dominant models. Allele frequencies at the VDR BsmI polymorphism from the respective studies were determined by the allele counting method. The pooled odds ratio (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the relationship between VDR BsmI polymorphism and periodontitis risk. The Z-test was used to determine the significance of the pooled ORs and 95% CIs. The between-study heterogeneity was assessed by chi-squarebased Q-test.(7) In cases of heterogeneity, the random-effects model was chosen to pool ORs with 95%CIs, otherwise the fixed-effects model was used. Sensitivity analysis was performed by comparing the results of fixed-effects model and random-effects model. All statistical tests were performed using the Stata, version 12 (StataCorp LP, College Station, TX). A P value less than 0.05 was considered to be statistically significant.

Results

Description of included studies

Figure 1 graphically illustrates the trial flow chart. A total of 75 articles that examined the association between VDR polymorphisms and risk of periodontitis were identified in different databases. According to the inclusion criteria, 6 articles (8-13) with 757 periodontitis cases and 670 controls were included in this meta-analysis at last. The publication year of involved studies ranged from 2005 to 2015. The source of controls in five studies was population-based. Characteristics of included studies are summarized in Table 1.

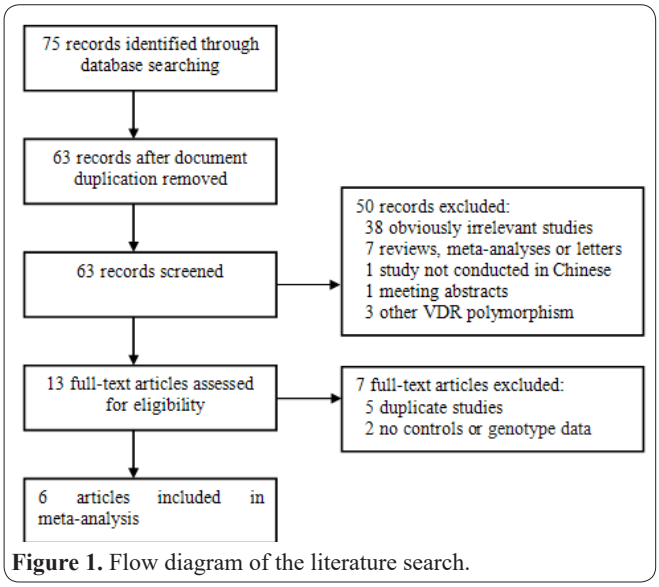

Figure 1. Flow diagram of the literature search.

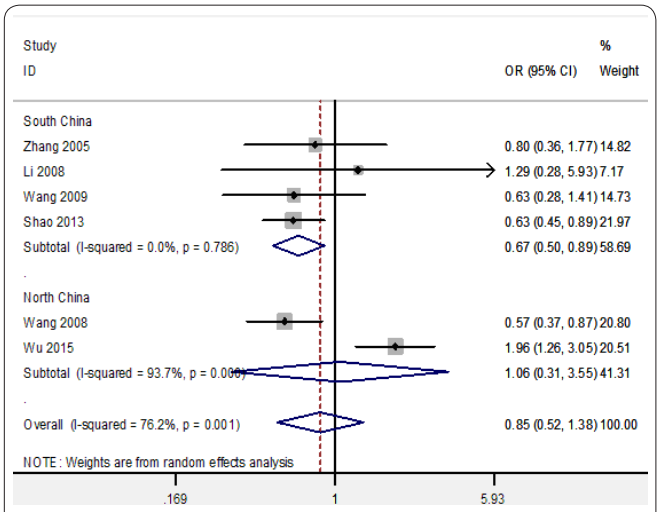

Figure 2. The forest plots of all selected studies on the association between VDR BsmI polymorphism and periodontitis risk in Chinese (for allele model b vs. B).

Meta-analysis

Table 2 lists the primary results. First, a heterogeneity analysis was conducted, and no association was found between VDR BsmI polymorphism and the risk of periodontitis in the total analyses (Figure 2). Cumulative

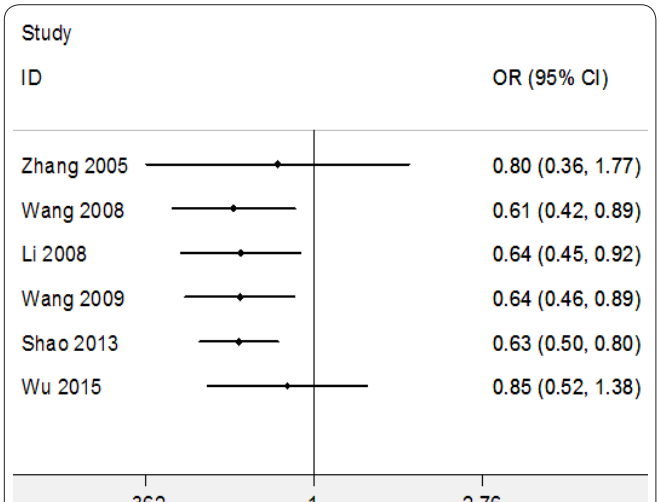

Figure 3. Cumulative analysis of the relationship between VDR BsmI polymorphism and periodontitis risk in Chinese (for allele model b vs. B).

Table 2. Association of the VDR BsmI gene polymorphism on periodontitis susceptibility.

Analysis model		n	ORr(95%CI)	ORf(95%CI)	P_h
b vs. B	Total analysis	6	0.85 (0.52-1.38)	0.82 (0.67-1.01)	0.001
	Population-based	5	0.86 (0.49-1.51)	0.82 (0.67-1.02)	0.000
	South China	4	**0.67 (0.50-0.89)**	**0.67 (0.50-0.89)**	0.786
	North China	2	1.06 (0.31-3.55)	1.03 (0.76-1.39)	0.000
	CP	5	0.82 (0.49-1.38)	0.82 (0.66-1.00)	0.000
bb vs. BB	Total analysis	4	0.95 (0.45-2.03)	0.80 (0.57-1.13)	0.018
	Population-based	3	0.91 (0.40-2.06)	0.79 (0.56-1.12)	0.008
	South China	2	0.68 (0.42-1.11)	0.68 (0.42-1.11)	0.442
	North China	2	1.14 (0.25-5.28)	0.95 (0.58-1.55)	0.003
	CP	4	0.95 (0.45-2.03)	0.80 (0.57-1.13)	0.018
bb vs. BB+Bb	Total analysis	6	0.85 (0.50-1.45)	0.83 (0.64-1.09)	0.006
	Population-based	5	0.88 (0.47-1.65)	0.85 (0.64-1.1.2)	0.003
	South China	4	**0.64 (0.45-0.92)**	**0.64 (0.45-0.92)**	0.789
	North China	2	1.16 (0.29-4.63)	1.16 (0.77-1.73)	0.001
	CP	5	0.82 (0.46-1.46)	0.82 (0.63-1.08)	0.003
bb+Bb vs.BB	Total analysis	4	0.87 (0.49-1.55)	0.79 (0.56-1.11)	0.089
	Population-based	3	0.84 (0.45-1.57)	0.78 (0.55-1.10)	0.049
	South China	2	0.70 (0.43-1.15)	0.70 (0.43-1.14)	0.437
	North China	2	0.99 (0.31-3.20)	0.88 (0.55-1.41)	0.019
	CP	4	0.87 (0.49-1.55)	0.79 (0.56-1.11)	0.089

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; P_h *P* value for heterogeneity test; North China included Liaoning, Xinjiang; South China included Sichuan, Jiangsu, Guangdong, Yunnan.

analysis further suggested a lack association between VDR BsmI polymorphism and the risk of periodontitis in the Chinese population (Figure 3). However, in the subgroup analyses by geographic area(s), source of controls and type of periodontitis, significant results of the association between the VDR BsmI variants and periodontitis were found in South China (b vs. B, OR=0.67, CI=0.50-0.89; bb vs. BB+Bb, OR=0.64, CI=0.45-0.92).

Sensitivity analysis

Sensitivity analyses were performed by comparing the results of fixed-effects model and random-effects model. All the corresponding ORs did not materially alter under all models, suggesting that the results of this meta-analysis are stable (Table 2).

Discussion

Due to the central role of VDR in the development of periodontitis and the different function between the VDR BsmI B and the b allele, it has been hypothesized that VDR BsmI polymorphism is associated with risk of periodontitis, and many reports have been published but no clear consensus has been reached. This led us to undertake the present meta-analysis, which could quantitate the synthesis of all the available data and might help us to explore a more robust estimate of the role of this polymorphism with periodontitis in a single ethnic group. The main finding of our pooled analysis of 6 case–control studies, including 757 cases and 670 controls, was that the VDR BsmI b allele is associated with a significantly reduced risk of periodontitis in South China.

In the past, a number of studies were performed to investigate the association between VDR BsmI variants and periodontitis. Several studies (12-15) found that the VDR BsmI polymorphism was associated with increased risk of developing CP, while the opposite results were also found with the generalized aggressive periodontitis and severe generalized CP in some ones (16-18). These evidence was consistent with our findings, which indicated the association between VDR BsmI variants and periodontitis might be due to not only the ethnic background, regions, and sample size, but also the different mechanisms of CP and AP.

As compared to a previous meta-analysis by Deng et al. (19), which included four case-control study in China, our meta-analysis contained more researches conducted in the Chinese population. Furthermore, in another meta-analysis conducted by Chen et al. (20), two studies (10, 21) might involve duplicate subjects in the Chinese population. This current meta-analysis is strengthened by excluding the reduplication, which revealed the significant results in subgroup analyses. The effects of gene-environment interactions with respect to periodontitis risk were determined by subgroup analyses. We were able to explore the association between VDR BsmI polymorphism and periodontitis may not be influenced by genetic backgrounds and living environment. Sensitivity analyses confirmed the reliability and stability of the meta-analysis. Therefore, our results indicated that VDR BsmI polymorphism is associated with periodontitis in individuals from South China.

There may be some limitations to this study. First, the ethnic-specific meta-analysis only included data from a single ethnic group, and thus, our results are only applicable to this ethnic group. Second, the results were based on unadjusted estimates. A more precise analysis should be conducted with individual data. We were not capable of conducting these analyses due to the lack of sufficient data from the primary studies. Third, the heterogeneity was high and it was not explained by stra-

tification analyses. Other clinical heterogeneity might contribute to it, such as diagnosis and classification of periodontal disease, differences on the periodontal examination, and by different clinicians; however, we could not explore them due to the limited data of included studies. Finally, due to the limitations of funnel plotting, which requires a range of studies, we did not evaluate publication bias in this meta-analysis.

In conclusion, this meta-analysis indicates that VDR BsmI polymorphism was not associated with the decreased risk of periodontitis in Chinese individuals from South China. However, more studies should be conducted in the future to validate our findings.

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Conflicts of interest
There are no conflicts of interest.

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