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Assessment of the link between Vitamin D receptor *Taq*I gene polymorphism and periodontitis: a meta-analysis in a Chinese population

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ABSTRACT. Although a number of studies have been conducted to determine the association between vitamin D receptor (VDR) *Taq*I polymorphism and periodontitis in the Chinese population, this association remains elusive. To assess the influence of VDR *Taq*I polymorphism on the risk of periodontitis, a meta-analysis was performed in a Chinese population. Relevant studies were identified using the databases PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine, through January 2016. Pooled odds ratios and 95% confidence intervals were used to

assess the strength of the associations. This meta-analysis identified 9 studies, which included 1014 periodontitis cases and 907 controls. In both overall and subgroup analyses, VDR *Taq*I polymorphism was not associated with the risk of periodontitis. Cumulative analysis also suggested a lack of association between VDR *Taq*I polymorphism and the risk of periodontitis in the Chinese population. In conclusion, our meta-analysis showed that VDR *Taq*I polymorphism is not associated with the risk of periodontitis in the Chinese population. Further studies in other ethnic groups are required for definite conclusions.

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

INTRODUCTION

Periodontitis is a set of inflammatory diseases that affect the supporting tissues of the teeth. It manifests mainly as chronic periodontitis (CP) and aggressive periodontitis (AP) (Armitage, 1999). It has a high prevalence (10-15%), and is considered as one of the most widespread and complex inflammatory diseases in humans (Albandar and Rams, 2002). Periodontitis is a multi-factorial disease with both genetic and environmental risk factors. Many researchers have agreed that susceptibility to periodontal disease is at least partially due to genetic predisposition (Seymour, 1991). 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 located on chromosome 1p12. It is clear that mutations in functionally critical areas of the VDR gene can have profound effects on mineral metabolism and bone mineral density (Lin et al., 1996; Malloy et al., 1997). Several VDR gene polymorphisms have been identified, and the *Taq*I (or rs731236) single nucleotide polymorphism has been extensively studied. Hennig et al. (1999) found an association between VDR *Taq*I polymorphism and localized early-onset periodontal diseases in a Caucasian population. As a result, many studies have attempted to clarify this relationship. However, no definite consensus has been reached. The differences in results may be due to ethnic and clinical heterogeneity among the subjects of a study, as well as the relatively small sample size of each study. Meta-analysis is one way to overcome the inadequate sample size for a statistical analysis. To better understand the association between VDR *Taq*I polymorphism and periodontitis, we performed a meta-analysis of all eligible studies in the Chinese population only, which can reduce the impact of differences in genetic background.

MATERIAL AND METHODS

Search strategy and selection criteria

Literature searches were conducted all through January 2016 using the following databases: PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine. The search keywords used were periodontitis or periodontal disease, vitamin D receptor or VDR, and China or Chinese or Taiwan. Searches were performed with no language restrictions, and

were limited to human studies. References within the retrieved articles were also examined for relevant studies.

The inclusion criteria for the meta-analysis were as follows: 1) case-control or cohort studies describing the association between VDR *Taq*I polymorphism and periodontitis, 2) clear description of VDR *Taq*I polymorphism in periodontitis patients and control, 3) Chinese participants only. The exclusion criteria were 1) duplicate publications; 2) incomplete data; 3) absence of controls; and 4) meta-analyses, letters, meeting abstracts, reviews, and editorial articles.

Data extraction

Two authors independently extracted information from all potential studies; disagreements were resolved by discussion. The titles and abstracts of all potentially relevant articles were screened to determine their relevance. Full articles were scrutinized if the title and abstract were ambiguous. Data extracted from identified studies included first author's name, publication year, type of periodontitis, ethnicity, source of controls, geographical area(s), sample size, and number of subjects with VDR *Taq*I genotypes.

Statistical analysis

The strength of the association between VDR *Taq*I polymorphisms and periodontitis susceptibility was estimated via pooled odds ratio (ORs) with 95% confidence intervals (CIs). The Z-test was used to determine the significance of the pooled ORs and 95%CIs. Genetic heterogeneity was tested by Q-statistics with P values < 0.10. In cases where genetic heterogeneity was present, the random-effect model was chosen to pool ORs with 95%CIs, otherwise, fixed-effect model was used. Sensitivity analysis was performed by excluding studies that were not in Hardy-Weinberg equilibrium (HWE) ($P < 0.05$). In addition, we stratified studies according to geographical location(s), source of controls, type of periodontitis, and ethnicity. All statistical analyses were carried out using the STATA version 10.0 (Stata Corporation, College Station, TX, USA) software. $P < 0.05$ was considered statistically significant.

RESULTS

Description of included studies

Figure 1 presents the trial flow chart. A total of 63 articles that investigated the association between VDR polymorphisms and risk of periodontitis were identified from various databases. After screening the titles and abstracts, 48 articles were excluded according to the exclusion criteria outlined earlier. Of the 15 potentially relevant articles (Tachi et al., 2001; Ma, 2002; Sun et al., 2002; Li et al., 2008; Wang, 2009; Yang et al., 2009; Zhang et al., 2005, 2010, 2011; Shao, 2013; Wang et al., 2009a,b, 2013; Cao et al., 2015; Wu et al., 2015) identified for full study retrieval, five studies (Tachi et al., 2001; Ma, 2002; Wang, 2009; Wang et al., 2009b; Yang et al., 2009) were excluded due to duplication; two studies were excluded due to lack of controls or genotype data (Wang et al., 2013; Cao et al., 2015). Finally, eight articles (including 9 case-control studies) (Sun et al., 2002; Li et al., 2008; Wang et al., 2009a;

Zhang et al., 2005, 2010, 2011; Shao, 2013; Wu et al., 2015) met the inclusion criteria. The publication year of these studies ranged from 2002 to 2015. In total, 1014 periodontitis cases and 907 controls were included in this meta-analysis. The source of controls in these studies was population-based. Characteristics of included studies are summarized in Table 1.

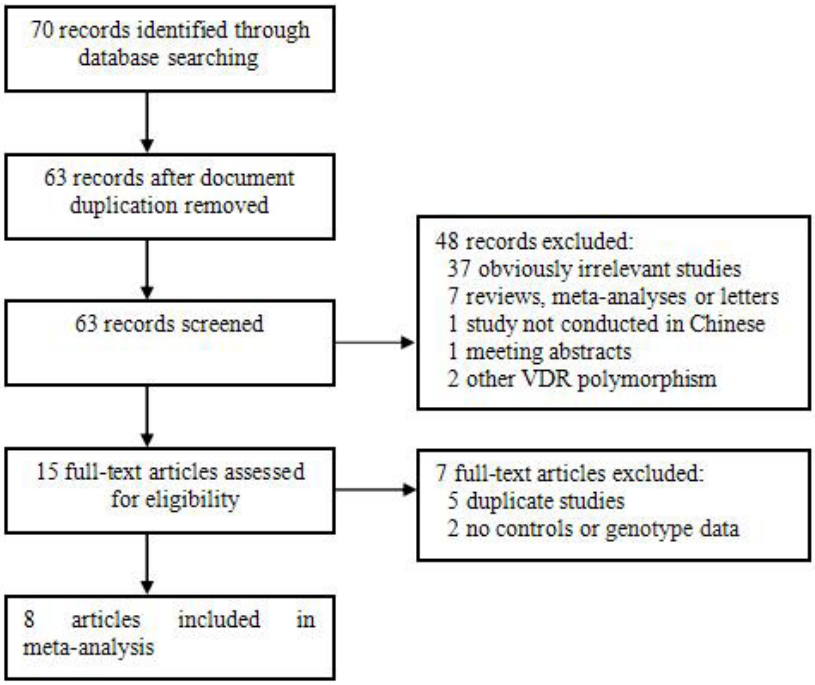

Figure 1. Flow diagram of the literature search.

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

References	Type of periodontitis	Ethnicity	Source of controls	Geographic area	Case number	Control number	Cases			Controls			HWE	
							TT	Tt	tt	TT	Tt	tt	χ^2	P
Sun et al., 2002	CP/AP	Han	PB	Beijing	61	39	51	10	0	37	2	0	0.03	0.869
Zhang et al., 2005	CP	Han	HB	Sichuan	166	80	145	21	0	71	9	0	0.28	0.594
Li et al., 2008	AP	Han	PB	Jiangsu	51	53	45	6	0	46	7	0	0.26	0.607
Wang et al., 2009a	CP	Han	PB	Guangdong	107	121	99	7	1	99	22	0	1.21	0.271
Zhang et al., 2010	CP/AP	Han	PB	Beijing	124	91	108	16	0	84	7	0	0.15	0.703
Zhang et al., 2011	CP	Hui	PB	Ningxia	88	92	83	5	0	78	14	0	0.62	0.430
Zhang et al., 2011	CP	Han	PB	Ningxia	90	95	84	6	0	79	16	0	0.80	0.370
Shao 2013	CP	Han	PB	Yunnan	232	246	165	3	64	185	5	56	219.19	0.000
Wu et al., 2015	CP	Uyghur	PB	Xinjiang	95	90	76	19	0	69	21	0	1.57	0.210

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

Meta-analysis

Table 2 listed the primary results. First, a heterogeneity analysis was conducted, and no association was found between VDR *Taq*I polymorphism and risk of periodontitis in the overall analyses (Figure 2). In the subgroup analyses stratified by geographical area(s),

source of controls, type of periodontitis, and ethnicity, there was no significant association between VDR *Taq*I variants and periodontitis. Cumulative analysis further suggested a lack of association between VDR *Taq*I polymorphism and risk of periodontitis in the Chinese population (Figure 3).

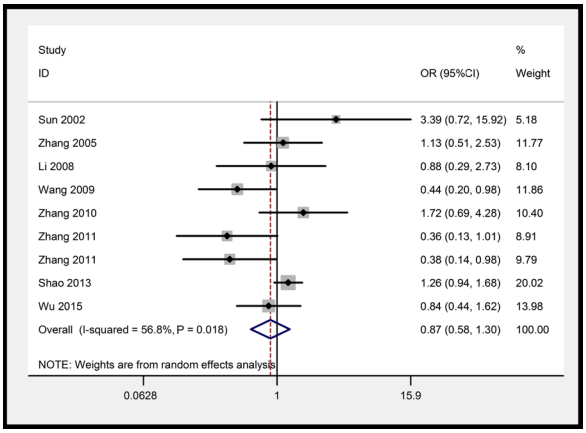

Figure 2. Forest plots of all selected studies on the association between VDR *Taq*I polymorphism and risk for periodontitis in the Chinese population (for allele model t *vs* T).

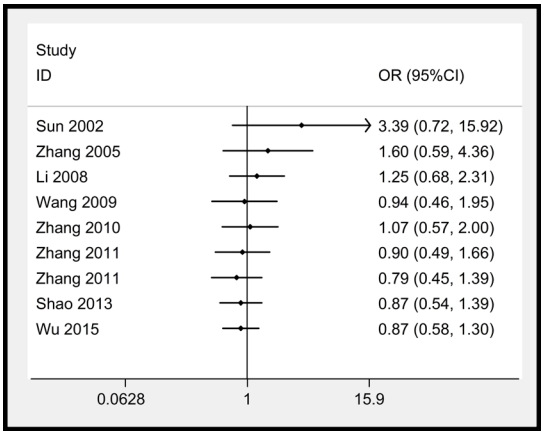

Figure 3. Cumulative analysis of the link between VDR *Taq*I polymorphism and risk for periodontitis in the Chinese population (for allele model t *vs* T).

Sensitivity analyses

Sensitivity analyses were performed by excluding the HWE-violating studies to evaluate the stability of the results. Violation from HWE was observed in the controls of one study (Table 1). After excluding the mentioned study, the corresponding ORs did not change significantly in any of the models, suggesting that the results of this meta-analysis were stable (Table 2).

Table 2. Association of VDR *Taq*I gene polymorphism with periodontitis susceptibility.

Analysis model		N	ORr (95%CI)	ORf (95%CI)	P_h
t *vs* T	Total analysis	9	0.87 (0.58-1.30)	1.00 (0.82-1.24)	0.018
	Population-based	8	0.84 (0.53-1.32)	1.00 (0.80-1.23)	0.010
	South China	4	0.93 (0.57-1.53)	1.09 (0.85-1.40)	0.107
	North China	5	0.84 (0.41-1.72)	0.82 (0.56-1.21)	0.029
	CP	6	0.71 (0.44-1.16)	0.94 (0.75-1.18)	0.012
	CP/AP	2	2.05 (0.94-4.49)	2.11 (0.97-4.58)	0.458
	Han	7	0.97 (0.61-1.54)	1.09 (0.87-1.36)	0.031
	In HWE	8	0.79 (0.50-1.26)	0.78 (0.58-1.06)	0.056
tt *vs* TT	Total analysis	2	1.30 (0.86-1.96)	1.30 (0.86-1.97)	0.607
tt *vs* TT + Tt	Total analysis	2	1.31 (0.87-1.98)	1.32 (0.87-1.99)	0.555
Tt + Tt *vs* TT	Total analysis	9	0.84 (0.54-1.30)	0.91 (0.71-1.16)	0.016
	Population-based	8	0.80 (0.49-1.32)	0.89 (0.69-1.15)	0.010
	South China	4	0.87 (0.50-1.53)	0.98 (0.71-1.34)	0.088
	North China	5	0.83 (0.39-1.79)	0.81 (0.54-1.21)	0.021
	CP	6	0.67 (0.40-1.11)	0.81 (0.62-1.06)	0.019
	CP/AP	2	2.14 (0.96-4.77)	2.19 (0.99-4.86)	0.444
	Han	7	0.94 (0.56-1.58)	1.00 (0.76-1.31)	0.022
	In HWE	8	0.77 (0.46-1.28)	0.76 (0.55-1.04)	0.031

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

DISCUSSION

Periodontitis is an inflammatory disease that is caused primarily by microorganisms; it is also a multifactorial disease. Convincing evidence suggests that an individual's susceptibility to periodontal disease is partially influenced by genetic predisposition. The link between VDR polymorphisms and risk for periodontitis attracted the attention of both doctors and researchers. However, a recent study found no statistically significant association between VDR polymorphism *Taq*I and periodontitis in a Han Chinese population (Wang et al., 2015). Two meta-analyses found significant associations between VDR *Taq*I variants and periodontitis rather than AP in Asians, but not in Caucasians (Deng et al., 2011; Chen et al., 2012). Regional and racial differences are other possible reasons for the contradicting results. Therefore, we conducted this meta-analysis to provide a more precise estimate on the association between VDR *Taq*I polymorphism and susceptibility to periodontitis in the Chinese population. Our meta-analysis involved nine case-control studies, including 1014 periodontitis cases and 907 controls. Results did not show any significant association between VDR *Taq*I polymorphism and periodontitis in both overall and subgroup analyses. To our knowledge, this study represents the first meta-analysis that examined the association between VDR *Taq*I variants and periodontitis in the Chinese population with such a large sample size.

The lack of association between VDR *Taq*I variants and risk for periodontitis in the Chinese population may be due to the following reasons: first, the racial and environmental differences among the different populations may be a highly significant factor; second, vitamin D and calcium were found to exert effects that were not limited to the spine and hip bones (Hildebolt, 2005). Therefore, excluding the vitamin D and calcium intake of all the participants, and other environmental factors, may have had an impact on our results. Moreover, multiple genes are often involved in complex diseases, and it is possible that a single gene is insufficient to result in periodontitis. Therefore, further studies should be performed

to address the following issues: 1) determination of the possible mechanisms behind the link between VDR and periodontitis, 2) subgroup analysis in terms of environment, classification, and severity of the disease.

In the past, a number of studies were performed to investigate the association between VDR *Taq*I variants and periodontitis. Brett et al. (2005) suggested that the *t* allele may be protective against periodontal diseases. Hennig et al. (1999) concluded that carriage of the less frequent t allele in VDR was associated with an increased risk for localized, but not generalized, disease. Sun et al. (2002) and Tachi et al. (2001) found that the VDR *Taq*I Tt genotype and the t allele may be a risk factor for aggressive periodontitis in Chinese patients, while the opposite genotype and allele were found to be associated with severe CP (Wang et al., 2009a). These evidences were consistent with our findings, which indicated that the association between VDR *Taq*I variants and periodontitis might be due to not only the ethnic background, regions, and sample size, but also the difference in mechanisms between CP and AP.

While our study was unique as we investigated the influence of ethnicity and geographical area(s) on the risk of periodontitis due to VDR *TaqI*, several limitations should be considered in our meta-analysis. First, the ethnic-specific meta-analysis only included data from Chinese patients with periodontitis, and thus, our results are only applicable to this ethnic group. Second, since this meta-analysis was based primarily on unadjusted effect estimates and CIs, confounding factors were not controlled. Third, heterogeneity was high, and was not explained by stratification analyses. Other clinical heterogeneity such as differential diagnosis and classification of periodontal disease, differences in periodontal examinations by clinicians may have also played a role in our results. However, we could not explore all the variables due to the limited data. Finally, due to limitations in 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 *Taq*I polymorphism was not associated with risk of periodontitis in the Chinese population. However, more studies should be conducted in the future to validate our findings.

Conflicts of interest

The authors declare no conflict of interest.

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