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Review Article

Association of vitamin D receptor BsmI, TaqI, FokI, and ApaI polymorphisms with susceptibility of chronic periodontitis: A systematic review and meta-analysis based on 38 case–control studies

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ABSTRACT

Background: There has been increasing interest in the study of the association between Vitamin D receptor (VDR) gene polymorphisms and risk of chronic periodontitis. However, the results remain inconclusive. To better understand the roles of VDR polymorphisms (BsmI, TaqI, FokI, and ApaI) in chronic periodontitis susceptibility, we conducted this systematic review and meta-analysis.

Materials and Methods: The PubMed, Google Scholar, and Web of Science database were systemically searched to determine all the eligible studies about VDR polymorphisms and risk of chronic periodontitis up to April 2017. Odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the associations between VDR polymorphisms and chronic periodontitis risk. All the statistical analyses were performed by Comprehensive Meta-Analysis. All *P* values were two-tailed with a significant level at 0.05.

Results: Finally, a total of 38 case–control studies in 19 publications were identified which met our inclusion criteria. There are ten studies with 866 chronic periodontitis cases and 786 controls for BsmI, 16 studies with 1570 chronic periodontitis cases and 1676 controls for TaqI, five studies with 374 chronic periodontitis cases and 382 controls for FokI, and seven studies with 632 chronic periodontitis cases and 604 controls for ApaI. Overall, no significant association was observed between VDR gene BsmI, TaqI, FokI, and ApaI polymorphisms and risk of chronic periodontitis in any genetic model. Subgroup analysis stratified by ethnicity suggested a significant association between BsmI polymorphism and chronic periodontitis risk in the Caucasian subgroup under allele model (A vs. G: OR = 1.747, 95% CI = 1.099–2.778, *P* = 0.018). Further, no significant associations were observed when stratified by Hardy–Weinberg equilibrium status for BsmI, TaqI, and ApaI.

Conclusion: Our results suggest that BsmI, TaqI, FokI, and ApaI polymorphisms in the VDR gene might not be associated with risk of chronic periodontitis in overall population.

Key Words: Chronic periodontitis, meta-analysis, polymorphism, Vitamin D receptor

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INTRODUCTION

Periodontal disease is the leading cause of tooth loss in the world, with chronic periodontitis the most common form representing the vast majority of all periodontal diseases.[1] Periodontal disease is highly prevalent and has multiple negative impacts on quality of life.[2] Chronic periodontitis is a reversible inflammation in response to intraoral plaque bacteria,[1,2] which affects the periodontal tissues resulting in irreversible apical migration of the junctional epithelium, loss of periodontal attachment, and ultimately tooth loss.[3,4] Periodontitis is a complex multifactorial disease that involves the interaction of genetic and environmental factors such as sex, age, smoking, and systemic diseases.[5,6] Among the genes suggested to be involved in periodontitis are genes that code for interleukin-1 (IL-1), IL-10, Vitamin D receptor (VDR), transforming growth factor beta (matrix metalloproteinase-3), IL-6, IL-1 β, tumor necrosis factor-alpha, etc.[7-11] The involvement of VDR gene polymorphisms have been suggested in the etiology of both aggressive and chronic periodontitis.[10] The gene-encoding VDR is localized to human chromosome 12q13-14 region and is spanned approximately 100 kb long, comprising at least five promoter regions, eight protein-coding exons, and six untranslated exons, which are alternatively spliced.[12-15] To date, several functional polymorphisms have been reported in the VDR genes, including FokI in exon 2 (C/T, rs10735810), BsmI in intron 8 (G/A, rs1544410), ApaI in intron 8 (A/C, rs7975232), Tru9 I in intron 8 (G/A, rs757343), and TaqI in exon 9 (T/C, rs731236).[16,17]

In 2001, Yoshihara *et al*. reported first association between the VDR gene BsmI G/A (rs1544410) polymorphism and aggressive periodontitis in a Japanese population.[18] Two years later, Tachi *et al*. reported associations between TaqI T/C (rs731236) and FokI C/T (rs2228570) polymorphisms and chronic periodontitis in the same population.[19] Later, the VDR polymorphisms susceptibility to chronic periodontitis have been investigated in different populations. Not surprisingly, the results obtained by different investigators vary. Therefore, to provide a more comprehensive assessment of the associations of the VDR polymorphisms (BsmI, TaqI, FokI, and ApaI) with chronic periodontitis, we carried out this systematic review and meta-analysis of all eligible studies published up to March 2017.

MATERIALS AND METHODS

Search Strategy

To identify eligible studies for this meta-analysis, we searched the MEDLINE (PubMed), Google Scholar, and Web of Science (Thomson-Reuters) for all eligible articles published up to March 20, 2017, that examined the association between the BsmI, TaqI, FokI, and ApaI polymorphisms of the VDR gene and chronic periodontitis risk. The following terms were included in the search: "periodontal disease," "chronic periodontitis," "Vitamin D receptor," "VDR," "BsmI (rs1544410, intron 8, +63980 G > A)," "TaqI (rs731236, exon 9, +65058 T > C)," "FokI (rs2228570, exon 2, +30920 C > T)," "ApaI (rs7975232, intron 8, +64978 C > A)," "polymorphism," "mutation," "variant," "gene," "genotype," "SNP," and "allele." The search was not restricted by the publication year or language. To identify potentially relevant studies, we manually searched reference lists of eligible studies, reviews, and related meta-analyses. In addition, we also contacted the authors to get more data as possible as we can. If there were multiple reports of the same study or overlapping data, only the study with the largest sample sizes or the most recent one was selected in our meta-analysis and the others were excluded.

Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: (1) full-text published studies; (2) epidemiological studies with case–control or cohort design; (3) investigating the association of VDR – BsmI, TaqI, FokI, and ApaI polymorphisms with chronic periodontitis risk; (4) providing sufficient genotype data or information that could help infer the results in the studies to calculate the odds ratios (ORs) with a 95% confidence interval (CI). The exclusion criteria were as follows: (1) studies with only case group (no control population), case reports, commentaries, and reviews; (2) studies on other polymorphisms of VDR gene; and (3) studies without detail genotype frequencies, which were unable to calculate OR.

Data extraction

Two investigators independently extracted data using a pre-designed form. For each study, the following information was extracted: name of first author, publication year, country where the study was conducted, ethnicity, polymorphisms, genotypic testing method, number of cases and controls, genotype frequency in cases and controls, minor allele frequencies (MAFs) in control subjects, and Hardy–Weinberg equilibrium

(HWE) test in control subjects. Diverse ethnicities were categorized as Caucasian, Asian, African, and Mixed, which included more than one race. Disagreements were resolved in consultation with the third reviewer.

Statistical analyses

All the statistical analyses were performed by Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood Cliffs, I.N.J., USA). All *P* values were two-tailed with a significant level at 0.05. The strength of associations was assessed using ORs and 95% CIs and the significance of pooled ORs was examined by Z_{test}. The pooled ORs were determined for BsmI under the allele (A vs. G), homozygote (AA vs. GG), heterozygote (AG vs. GG), dominant (AA + AG vs. GG), and recessive (AA vs. AG + GG) models. The TaqI was evaluated using the allele (C vs. T), homozygote (CC vs. TT), heterozygote (CT vs. TT), dominant (CC + CT vs. TT), and recessive (CC vs. CT + TT) models. The FokI polymorphism was assessed using the allele (T vs. C), homozygote (TT vs. CC), heterozygote (TC vs. CC), dominant (TT + TC vs. CC), and recessive (TT vs. TC + CC) models. The ApaI polymorphism was assessed using the allele model (T vs. G), homozygote (TT vs. GG), heterozygote (TG vs. GG), dominant model (TT + TG vs. GG), and recessive (TT vs. TG + GG) models. Heterogeneity between studies was evaluated by Cochran's *Q*-test and I^2 statistics. $P < 0.10$ or $I^2 > 50\%$ indicated significant heterogeneity. If substantial heterogeneity was detected, the random effects model (the DerSimonian-Laird method) was used; otherwise, the fixed effects model (the Mantel-Haenszel method) was utilized. Furthermore, to explore the source of between-study heterogeneity, subgroup analyses were performed. The one-way sensitivity analyses were performed to survey the stability of the results, namely, a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set to the pooled OR. Publication bias was examined using a Begg's funnel plot or Egger's plot, and the significance level was set at 0.05 for both. A HWE test of the VDR gene polymorphisms in healthy subjects was examined using Chi-square test and deviation was considered when $P < 0.01$.

RESULTS

Study characteristics

Initially, we have identified 52 publications through the database search. After reading the titles and abstracts, two publications with duplicate titles and four articles that were review articles or assessed unrelated diseases were excluded. Finally, a total of 38 case–control studies in 19 publications [13-15,20-34] were identified met our inclusion criteria. There are ten studies[13-15,20-26] with 866 chronic periodontitis cases and 786 concerning BsmI, 16 studies[13-15,19,21,23,26-34] with 1570 chronic periodontitis cases and 1676 controls concerning TaqI, five studies[19,20,23,25,26] with 374 chronic periodontitis cases and 382 controls concerning FokI, and seven studies[14,20,21,23-26] with 632 chronic periodontitis cases and 604 controls concerning ApaI. Main characteristics of the 38 included case–control studies were described in Table 1. Briefly, four main ethnic populations, including Caucasians, Asians, African, and Mixed, from eight countries were involved in this study. The countries of these studies included Brazil, China, Japan, Turkey, Jordan, Libya, Italy, India, and Colombia. The genotypes in control group for four case–control studies including two studies for BsmI,[21,22] one study for TaqI,[25] and one study for ApaI[33] were not consistent with HWE ($P < 0.05$). The characteristics of each study included in this meta-analysis are presented in Table 1.

Quantitative synthesis

Vitamin D receptor-BsmI polymorphism

The main results of BsmI polymorphism meta-analysis are shown in Table 2. The pooled results based on all included studies did not show a significant association between BsmI polymorphism and chronic periodontitis risk under all genetic models (allele model: A vs. G, OR = 1.159, 95% CI = 0.896–1.498, $P = 0.261$, Figure 1a; homozygote model: AA vs. GG, OR = 1.043, 95% CI = 0.738–1.475, $P = 0.810$; heterozygote model: AG vs. GG, OR = 1.182, 95% CI = 0.918–1.522, $P = 0.196$; dominant model: AA + AG vs. GG, OR = 1.174, 95% CI = 0.933–1.476, $P = 0.171$; and recessive model: AA vs. AG + GG, OR = 1.968, 95% CI = 0.702–1.334, $P = 0.842$). In the subgroup analyses, there was a significant association between BsmI polymorphism and chronic periodontitis risk only under the allele model (A vs. G: OR = 1.747, 95% C = 1.099–2.778, $P = 0.018$) in the Caucasian population, but not in Asian, Mixed, and African populations. When stratifying the studies by HWE status, the association between BsmI polymorphism and chronic periodontitis risk was not significant in all genetic models.

Table 1: Characteristics of studies included in Vitamin D receptor polymorphisms and chronic periodontitis

First Author	Country (Ethnicity)	Genotyping Technique	Case/ control	Cases					Controls					MAFs	HWE
				Genotypes			Allele		Genotypes			Allele			
BsmI G>A (rs1544410)				GG	AG	AA	G	A	GG	AG	AA	G	A		
de Brito Júnior, 2004[13]	Brazil (mixed)	PCR	69/44	16	43	10	75	63	18	18	8	54	34	0.386	0.362
Zhang, 2005[14]	China (Asian)	PCR-RFLP	166/80	144	21	1	309	23	72	7	1	151	9	0.056	0.115
de Souza, 2007[15]	Brazil (mixed)	PCR-RFLP	50/59	21	22	7	64	36	22	22	15	66	52	0.440	0.061
Naito, 2007[20]	Japan (Asian)	PCR	17/80	13	4	0	30	4	65	15	0	145	15	0.093	0.354
Gunes, 2008[21]	Turkey (Caucasian)	PCR-RFLP	72/102	29	33	10	91	53	42	51	9	135	51	0.274	0.003
Wang, 2008[22]	China (Asian)	PCR-RFLP	106/80	49	11	46	109	103	48	8	24	104	56	0.350	≤0.001
Wang, 2009[23]	China (Asian)	PCR-RFLP	107/121	92	15	0	199	15	110	11	0	231	11	0.045	0.600
Karasneh, 2013[24]	Jordan (Asian)	PCR-RFLP	94/123	34	45	15	113	75	37	56	30	130	116	0.471	0.337
El Jilani, 2015[25]	Libya (African)	Sequencing	75/47	21	47	7	89	61	18	26	3	62	32	0.340	0.111
Tobón-Arroyave, 2017[26]	Colombian (mixed)	PCR-RFLP	110/50	50	45	15	145	75	18	23	9	59	41	0.410	0.728
TaqI T>C (rs731236)				TT	CT	CC	T	C	TT	CT	CC	T	C		
Tachi, 2003[19]	Japan (Asian)	PCR-RFLP	74/94	66	8	0	140	8	72	22	0	166	22	0.117	0.198
de Brito Júnior, 2004[13]	Brazil (mixed)	PCR	69/44	23	41	5	87	51	24	14	6	62	26	0.295	0.117
Zhang, 2005[14]	China (Asian)	PCR-RFLP	166/80	145	21	0	311	21	71	9	0	151	9	0.056	0.594
de Souza, 2007[15]	Brazil (mixed)	PCR-RFLP	50/59	20	24	6	64	36	23	29	7	75	43	0.364	0.638
Gunes, 2008[21]	Turkey (Caucasian)	PCR-RFLP	72/102	36	28	8	100	44	48	47	7	143	61	0.299	0.316
Nibali, 2008[27]	UK (Caucasian)	PCR-RFLP	79/231	27	24	7	78	38	53	63	28	169	119	0.413	0.240
Borges, 2009[28]	Brazil (mixed)	PCR-RFLP	30/30	7	18	5	32	28	16	9	5	41	19	0.316	0.092
Wang, 2009[23]	China (Asian)	PCR-RFLP	107/121	99	7	1	205	9	99	22	0	220	22	0.090	0.271
Zhang, 2010[29]	China (Asian)	PCR-RFLP	34/91	33	1	0	67	1	84	7	0	175	7	0.038	0.702
Zhang, 2011[30]	China (Asian)	PCR-RFLP	178/187	167	11	0	345	11	157	30	0	344	30	0.080	0.233
Martelli, 2011[31]	Italy (Caucasian)	TaqMan	115/65	41	60	14	142	88	15	30	20	60	70	0.538	0.564
Karasneh, 2013[24]	Jordan (Asian)	PCR-RFLP	99/126	40	44	15	124	74	41	60	25	142	110	0.436	0.719
Kaarthikeyan, 2013[32]	India (Asian)	PCR-RFLP	60/60	23	26	11	72	48	37	19	4	93	27	0.225	0.476
Shao, 2013[33]	China (Asian)	PCR-RFLP	232/246	165	3	64	333	131	185	5	56	375	117	0.237	≤0.001
Wu, 2015[34]	China (Asian)	PCR-RFLP	95/90	76	19	0	171	19	69	21	0	159	21	0.116	0.210
Tobón-Arroyave, 2017[26]	Colombian (mixed)	PCR-RFLP	110/50	53	47	10	153	67	21	24	5	66	34	0.340	0.623
FokI C>T (rs2228570)				CC	TC	TT	C	T	CC	TC	TT	C	T	CC	
Tachi, 2003[19]	Japan (Asian)	PCR-RFLP	74/94	28	35	11	91	57	43	38	13	124	64	0.340	0.333
Naito, 2007[20]	Japan (Asian)	PCR	17/80	4	4	9	12	22	15	40	25	70	90	0.562	0.887
Wang, 2009[23]	China (Asian)	PCR-RFLP	107/121	29	62	16	120	94	37	65	19	139	103	0.425	0.277
El Jilani, 2015[25]	Libya (African)	Sequencing	66/37	38	27	1	103	29	21	13	3	55	19	0.256	0.629
Tobón-Arroyave, 2017[26]	Colombian (mixed)	PCR-RFLP	110/50	42	54	14	138	82	16	28	6	60	40	0.400	0.238
ApaI G>T (rs7975232)				GG	TG	TT	G	T	GG	TG	TT	G	T	GG	
Zhang, 2005[14]	China (Asian)	PCR-RFLP	166/80	61	74	31	196	136	6	31	43	43	117	0.731	0.899
Naito, 2007[20]	Japan (Asian)	PCR	17/80	12	3	2	27	7	38	33	9	109	51	0.318	0.653
Gunes, 2008[21]	Turkey (Caucasian)	PCR-RFLP	72/102	33	23	16	89	55	40	43	19	123	81	0.397	0.227
Wang, 2009[23]	China (Asian)	PCR-RFLP	107/121	11	51	45	73	141	20	46	55	86	156	0.644	0.061
Karasneh, 2013[24]	Jordan (Asian)	PCR-RFLP	99/126	35	47	17	117	81	52	56	18	160	92	0.365	0.642
El Jilani, 2015[25]	Libya (African)	Sequencing	61/45	10	43	8	63	59	7	33	5	47	43	0.477	0.001
Tobón-Arroyave, 2017[26]	Colombian (mixed)	PCR-RFLP	110/50	19	64	27	102	118	5	25	20	35	65	0.650	0.484

PCR: Polymerase chain reaction-restriction; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism MAFs: Minor allele frequencies; HWE: Hardy-Weinberg equilibrium.

Vitamin D receptor-TaqI polymorphism

The main results of this meta-analysis are shown in Table 3. Overall, no significant associations were found between TaqI polymorphism and chronic periodontitis risk when all studies were pooled into the meta-analysis under all genetic models (allele model: C vs. T: OR = 0.946, 95% C = 0.828–1.080, $P = 0.408$; homozygote model: CC vs. TT: OR = 0.951, 95% CI = 0.602–1.503, $P = 0.831$, Figure 1b; heterozygote model: CT vs. TT: OR = 0.857, 95% CI = 0.619–1.185, $P = 0.350$; the dominant model: CC + CT vs. TT: OR = 0.979, 95% CI = 0.577–1.660, $P = 0.937$; recessive model: CC vs. CT + TT: OR = 0.941, 95% CI = 0.729–1.214, $P = 0.638$). In the subgroup analyses by ethnicity, there was no a significant association between TaqI polymorphism and chronic

Table 2: The meta-analysis of BsmI A/G (rs1544410) polymorphism and chronic periodontitis risk

Subgroup	Study number	Genetic Model	Type of model	Heterogeneity		OR				Publication Bias	
				I_2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	9	A vs. G	Random	52.98	0.024	1.159	0.896-1.498	1.123	0.261	1.000	0.643
	8	AA vs. GG	Fixed	36.76	0.136	1.043	0.738-1.475	0.240	0.810	1.000	0.639
	10	AG vs. GG	Fixed	0.00	0.510	1.182	0.918-1.522	1.294	0.196	0.283	0.107
	10	AA+AG vs. GG	Fixed	20.95	0.250	1.174	0.933-1.476	1.369	0.171	0.591	0.375
	8	AA vs. AG + GG	Fixed	32.08	0.172	1.968	0.702-1.334	−0.200	0.842	1.000	0.577
By Ethnicity											
Caucasian	1	A vs. G	Reference	0.00	1.000	1.747	1.099-2.778	2.358	0.018	NA	NA
	1	AA vs. GG	Reference	0.00	1.000	1.609	0.582-4.451	0.917	0.359	NA	NA
	1	AG vs. GG	Reference	0.00	1.000	0.937	0.492-1.786	−0.197	0.843	NA	NA
	1	AA + AG vs. GG	Reference	0.00	1.000	1.038	0.562-1.918	0.119	0.905	NA	NA
	1	AA vs. AG + GG	Reference	0.00	1.000	1.667	0.641-4.336	1.047	0.295	NA	NA
Asian	5	A vs. G	Random	57.76	0.050	1.231	0.800-1.895	0.945	0.345	1.000	0.628
	3	AA vs. GG	Random	67.76	0.045	0.956	0.339-2.698	−0.085	0.932	1.000	0.732
	5	AG vs. GG	Fixed	0.00	0.758	1.209	0.830-1.763	0.989	0.323	0.806	0.197
	5	AA + AG vs. GG	Fixed	13.51	0.328	1.249	0.902-1.730	1.338	0.181	0.806	0.641
	3	AA vs. AG + GG	Fixed	66.16	0.052	1.070	0.681-1.682	0.295	0.768	1.000	0.780
Mixed	3	A vs. G	Fixed	38.69	0.196	0.880	0.650-1.190	−0.831	0.406	1.000	0.703
	3	AA vs. GG	Fixed	0.00	0.380	0.717	0.388-1.325	−1.062	0.288	1.000	0.520
	3	AG vs. GG	Fixed	62.98	0.067	1.172	0.735-1.870	0.666	0.505	0.296	0.334
	3	AA + AG vs. GG	Fixed	63.14	0.066	1.014	0.656-1.567	0.061	0.951	0.296	0.328
	3	AA vs. AG + GG	Fixed	0.00	0.773	0.643	0.368-1.123	−1.551	0.121	1.000	0.852
African	1	A vs. G	Reference	0.00	1.000	1.328	0.776-2.27	1.036	0.300	NA	NA
	1	AA vs. GG	Reference	0.00	1.000	2.000	0.450-8.891	0.911	0.362	NA	NA
	1	AG vs. GG	Reference	0.00	1.000	1.549	0.702-3.418	1.085	0.278	NA	NA
	1	AA+AG vs. GG	Reference	0.00	1.000	1.596	0.736-3.463	1.183	0.237	NA	NA
	1	AA vs. AG + GG	Reference	0.00	1.000	1.510	0.371-6.151	0.575	0.565	NA	NA
By HWE											
	8	A vs. G	Fixed	20.78	0.265	0.954	0.782-1.166	−0.457	0.648	0.710	0.104
	6	AA vs. GG	Fixed	0.00	0.507	0.710	0.452-1.116	−1.482	0.138	0.132	0.478
	8	AG vs. GG	Fixed	8.19	0.367	1.224	0.919-1.629	1.382	0.167	0.386	0.206
	8	AA + AG vs. GG	Fixed	24.68	0.232	1.104	0.841-1.450	0.714	0.475	0.386	0.139
	6	AA vs. AG + GG	Fixed	0.00	0.848	0.666	0.442-1.003	−1.945	0.052	0.452	0.588

OR: Odds Ratio; CI: Confidence Interval; NA: Not Applicable; HWE: Hardy–Weinberg Equilibrium.

periodontitis risk in Caucasian, Asians, African, and Mixed populations. No significant associations were observed when stratified by HWE status.

Vitamin D receptor-FokI polymorphism

The main results of FokI polymorphism meta-analysis are shown in Table 4. The overall analyses suggested no significant association between the FokI and chronic periodontitis susceptibility in all genetic models (allele model: T vs. C: OR = 1.051, 95% CI = 0.842–1.311, $P = 0.660$; homozygote model: TT vs. CC: OR = 1.041, 95% CI = 0.638–1.699, $P = 0.873$; heterozygote model: TC vs. CC: OR = 1.062, 95% CI = 0.758–1.489, $P = 0.725$; the dominant model: TT + TC vs. CC: OR = 1.061, 95% CI = 0.771–1.462, Figure 1c, $P = 0.716$; recessive model: TT vs. TC + CC: OR = 1.107, 95% CI = 0.716–1.711, $P = 0.647$). In the subgroup analyses, there was no significant association between FokI polymorphism and chronic periodontitis risk in the Asians, African, and Mixed populations.

Vitamin D receptor-ApaI polymorphism

Table 5 gives the summary results for the association of the ApaI with the risk of chronic periodontitis based on all five genetic models. However, there was no significant association between the ApaI and chronic periodontitis susceptibility under all genetic models (allele model: T vs. G: OR = 0.737, 95% CI = 0.469–1.157, $P = 0.184$; homozygote model: TT vs. GG: OR = 0.674, 95% CI = 0.273–1.667, $P = 0.394$; heterozygote model: TG vs. GG: OR = 0.733, 95% CI = 0.424–1.268, $P = 0.266$; the dominant model: TT + TG vs. GG: OR = 0.670, 95% CI = 0.363–1.240, $P = 0.202$; recessive model: TT vs. TG + GG: OR = 0.729, 95% CI = 0.402–1.321, $P = 0.297$, Figure 1d). We then performed stratified

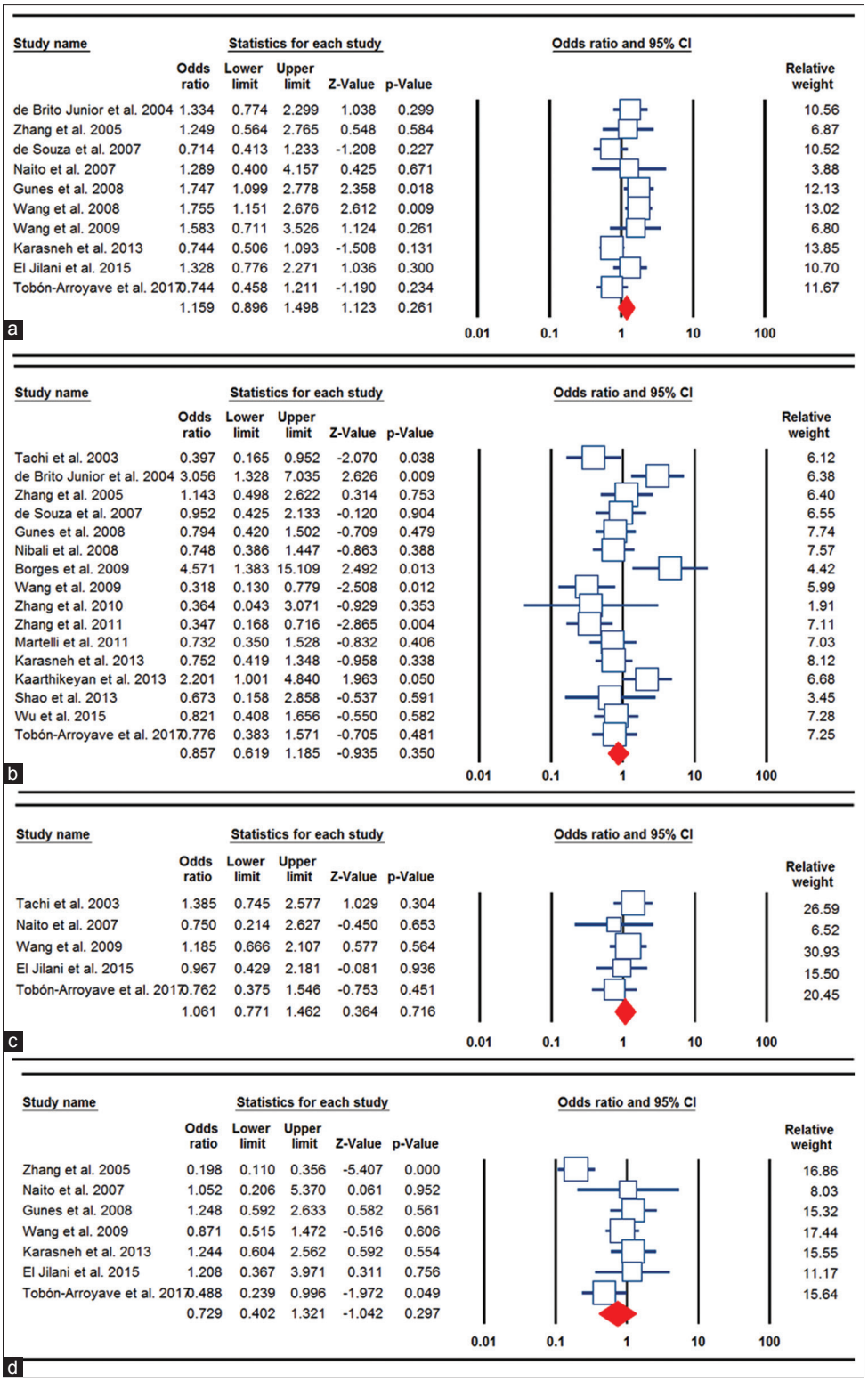

Figure 1: Forest plots for the association of the Vitamin D receptor polymorphisms and chronic periodontitis susceptibility. (a) BsmI (allele model: A vs. G); (b) TaqI (heterozygote model: CT vs. TT); (c) FokI (dominant model: TT + TC vs. CC); and (d) ApaI (recessive model: TT vs. TG + GG).

analysis by ethnicity and found a significant association between the ApaI polymorphism and chronic periodontitis risk in the mixed population under recessive model (TT vs. TG + GG: OR = 0.488, 95% CI = 0.239–0.996, P = 0.049), but not in the Caucasian, Asian, and African populations. Moreover,

Table 3: The meta-analysis of TaqI T/C (rs731236) polymorphism and chronic periodontitis risk

Subgroup	Study number	Genetic model	Type of model	Heterogeneity		OR				Publication Bias	
				I_2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	16	C vs. T	Random	82.28	≤0.001	0.946	0.828-1.080	−0.827	0.408	0.752	0.722
	11	CC vs. TT	Random	53.37	0.018	0.951	0.602-1.503	−0.214	0.831	0.275	0.923
	16	CT vs. TT	Random	60.01	0.001	0.857	0.619-1.185	−0.935	0.350	0.752	0.710
	16	CC + CT vs. TT	Random	87.36	≤0.001	0.979	0.577-1.660	0.079	0.937	0.821	0.968
	11	CC vs. CT + TT	Fixed	44.59	0.054	0.941	0.729-1.214	−0.470	0.638	0.533	0.956
By Ethnicity											
Caucasian	3	C vs. T	Random	95.50	≤0.001	1.256	0.337-4.685	0.339	0.734	1.000	0.141
	3	CC vs. TT	Random	66.80	0.049	0.553	0.207-1.479	−1.180	0.238	0.296	0.102
	3	CT vs. TT	Fixed	0.00	0.985	0.760	0.515-1.122	−1.381	0.167	0.296	0.367
	3	CC + CT vs. TT	Random	96.05	≤0.001	0.313	0.048-2.024	−1.220	0.222	0.296	0.176
	3	CC vs. CT + TT	Random	69.66	0.037	0.680	0.267-1.736	−0.806	0.420	0.296	0.102
Asian	9	C vs. T	Random	77.76	≤0.001	0.757	0.490-1.169	−1.257	0.209	0.348	0.170
	4	CC vs. TT	Fixed	59.42	0.060	1.227	0.865-1.740	1.145	0.252	0.734	0.660
	9	CT vs. TT	Random	56.24	0.019	0.674	0.435-1.045	−1.762	0.078	0.602	0.657
	9	CC + CT vs. TT	Random	81.05	≤0.001	1.193	0.645-2.208	0.563	0.574	0.754	0.911
	4	CC vs. CT + TT	Fixed	39.76	0.173	1.223	0.870-1.719	1.159	0.246	0.734	0.600
Mixed	4	C vs. T	Fixed	10.38	0.341	1.062	0.797-1.414	0.410	0.682	0.308	0.175
	4	CC vs. TT	Fixed	0.00	0.728	1.043	0.544-2.000	0.128	0.898	0.308	0.072
	4	CT vs. TT	Random	71.91	0.014	1.663	0.738-3.751	1.226	0.220	0.308	0.205
	4	CC + CT vs. TT	Random	68.30	0.024	1.471	0.714-3.031	1.046	0.296	0.089	0.202
	4	CC vs. CT + TT	Fixed	0.00	0.839	0.776	0.426-1.412	−0.831	0.406	1.000	0.934
By HWE											
	15	C vs. T	Random	82.47	≤0.001	0.891	0.614-1.294	-0.607	0.544	1.000	0.875
	10	CC vs. TT	Random	51.56	0.029	0.910	0.533-1.555	-0.343	0.731	0.049	0.076
	15	CT vs. TT	Random	62.59	0.001	0.865	0.617-1.211	-0.847	0.397	0.620	0.617
	15	CC + CT vs. TT	Random	88.05	≤0.001	0.966	0.532-1.756	-0.112	0.911	0.620	0.838
	10	CC vs. CT + TT	Fixed	37.51	0.109	0.831	0.541-1.278	-0.841	0.400	0.210	0.117

OR: Odds Ratio; CI: Confidence Interval; HWE: Hardy-Weinberg Equilibrium.

Table 4: The meta-analysis of FokI C/T (rs2228570) polymorphism and chronic periodontitis risk

Subgroup	Study number	Genetic Model	Type of Model	Heterogeneity		OR				Publication Bias	
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	5	T vs. C	Fixed	0.00	0.734	1.051	0.842-1.311	0.439	0.660	1.000	0.961
	5	TT vs. CC	Fixed	0.00	0.631	1.041	0.638-1.699	0.159	0.873	0.462	0.133
	5	TC vs. CC	Fixed	0.00	0.441	1.062	0.758-1.489	0.351	0.725	0.220	0.135
	5	TT+TC vs. CC	Fixed	0.00	0.729	1.061	0.771-1.462	0.364	0.716	0.462	0.259
	5	TT vs. TC+CC	Fixed	17.88	0.301	1.107	0.716-1.711	0.459	0.647	1.000	0.482
By Ethnicity											
Asian	3	T vs. C	Fixed	0.00	0.758	1.152	0.881-1.506	1.033	0.302	0.296	0.247
	3	TT vs. CC	Fixed	0.00	0.939	1.198	0.684-2.099	0.630	0.528	1.000	0.463
	3	TC vs. CC	Fixed	20.62	0.284	1.179	0.771-1.805	0.759	0.448	1.000	0.214
	3	TT+TC vs. CC	Fixed	0.00	0.688	1.207	0.809-1.800	0.920	0.357	1.000	0.343
	3	TT vs. TC+CC	Fixed	11.16	0.324	1.215	0.743-1.987	0.775	0.439	0.296	0.214
African	1	T vs. C	Reference	0.00	1.000	0.815	0.419-1.584	−0.603	0.546	NA	NA
	1	TT vs. CC	Reference	0.00	1.000	0.184	0.018-1.884	−1.426	0.154	NA	NA
	1	TC vs. CC	Reference	0.00	1.000	1.148	0.491-2.684	0.318	0.318	NA	NA
	1	TT+TC vs. CC	Reference	0.00	1.000	0.967	0.429-2.181	−0.081	0.936	NA	NA
	1	TT vs. TC+CC	Reference	0.00	1.000	0.174	0.017-1.741	−1.488	0.137	NA	NA
Mixed	1	T vs. C	Reference	0.00	1.000	0.891	0.549-1.447	−0.465	0.642	NA	NA
	1	TT vs. CC	Reference	0.00	1.000	0.889	0.291-2.714	−0.207	0.836	NA	NA
	1	TC vs. CC	Reference	0.00	1.000	0.735	0.352-1.532	−0.822	0.411	NA	NA
	1	TT+TC vs. CC	Reference	0.00	1.000	0.762	0.375-1.546	−0.753	0.451	NA	NA
	1	TT vs. TC+CC	Reference	0.00	1.000	1.069	0.385-2.968	0.129	0.897	NA	NA

OR: Odds Ratio; CI: Confidence Interval; NA: Not Applicable.

Table 5: The meta-analysis of ApaI G/T (rs7975232) polymorphism and chronic periodontitis risk

Subgroup	Study number	Genetic Model	Type of Model	Heterogeneity		OR				Publication Bias	
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	7	T vs. G	Random	84.45	≤0.001	0.737	0.469-1.157	−1.328	0.184	0.367	0.782
	7	TT vs. GG	Random	81.64	≤0.001	0.674	0.273-1.667	−0.853	0.394	0.229	0.624
	7	TG vs. GG	Random	63.02	0.013	0.733	0.424-1.268	−1.112	0.266	0.367	0.265
	7	TT + TG vs. GG	Random	74.74	0.001	0.670	0.363-1.240	−1.275	0.202	0.229	0.261
	7	TT vs. TG + GG	Random	75.98	≤0.001	0.729	0.402-1.321	−1.042	0.297	1.000	0.482
By Ethnicity										NA	NA
Caucasian	1	T vs. G	Reference	0.00	1.000	0.938	0.606-1.454	−0.285	0.776	NA	NA
	1	TT vs. GG	Reference	0.00	1.000	1.465	0.632-3.392	0.890	0.373	NA	NA
	1	TG vs. GG	Reference	0.00	1.000	0.548	0.327-1.286	−1.240	0.215	NA	NA
	1	TT + TG vs. GG	Reference	0.00	1.000	0.762	0.414-1.404	−0.870	0.384	NA	NA
	1	TT vs. TG + GG	Reference	0.00	1.000	1.248	0.592-2.633	0.582	0.561	NA	NA
Asian	4	T vs. G	Random	91.56	≤0.001	0.660	0.298-1.463	−1.023	0.306	0.308	0.802
	4	TT vs. GG	Random	89.29	≤0.001	0.571	0.127-2.574	−0.730	0.466	0.308	0.748
	4	TG vs. GG	Random	80.55	0.001	0.694	0.258-1.872	−0.721	0.471	0.734	0.368
	4	TT + TG vs. GG	Random	87.00	≤0.001	0.609	0.200-1.855	−0.873	0.382	0.308	0.371
	4	TT vs. TG + GG	Random	84.99	≤0.001	0.651	0.252-1.683	−0.887	0.375	1.000	0.778
African	1	T vs. G	Reference	0.00	1.000	1.024	0.593-1.766	0.084	0.933	NA	NA
	1	TT vs. GG	Reference	0.00	1.000	1.120	0.256-4.905	0.150	0.880	NA	NA
	1	TG vs. GG	Reference	0.00	1.000	0.912	0.314-2.651	−0.169	0.866	NA	NA
	1	TT + TG vs. GG	Reference	0.00	1.000	0.939	0.328-2.693	−0.116	0.908	NA	NA
	1	TT vs. TG+GG	Reference	0.00	1.000	1.208	0.367-3.971	0.311	0.756	NA	NA
Mixed	1	T vs. G	Reference	0.00	1.000	0.623	0.382-1.016	−1.897	0.058	NA	NA
	1	TT vs. GG	Reference	0.00	1.000	0.355	0.113-1.113	−1.776	0.076	NA	NA
	1	TG vs. GG	Reference	0.00	1.000	0.674	0.227-2.000	−0.711	0.477	NA	NA
	1	TT + TG vs. GG	Reference	0.00	1.000	0.532	0.187-1.518	−1.180	0.238	NA	NA
	1	TT vs. TG + GG	Reference	0.00	1.000	0.488	0.239-0.996	−1.972	0.049	NA	NA
By HWE											
	6	T vs. G	Random	86.58	≤0.001	0.698	0.417-1.166	−1.375	0.169	0.259	0.699
	6	TT vs. GG	Random	84.56	≤0.001	0.627	0.227-1.728	−0.903	0.367	0.259	0.507
	6	TG vs. GG	Random	69.09	0.006	0.703	0.374-1.319	−1.099	0.272	0.452	0.263
	6	TT + TG vs. GG	Random	78.83	≤0.001	0.634	0.315-1.276	−1.277	0.202	0.132	0.228
	6	TT vs. TG + GG	Random	79.09	≤0.001	0.685	0.358-1.312	−1.141	0.254	0.707	0.627

OR: Odds Ratio; CI: Confidence Interval; NA: Not Applicable; HWE: Hardy–Weinberg Equilibrium

no significant associations were observed when stratified by HWE status.

Minor allele frequencies

We have calculated MAFs for controls from the corresponding genotype distribution. Frequencies of the BsmI G > A (rs1544410), TaqI T > C (rs731236), FokI C > T (rs2228570), and ApaI G > T (rs7975232) alleles were in range of 0.045–0.471, 0.038–0.436, 0.256–0.425, and 0.318–0.650, respectively. Moreover, the variant alleles had different representations among controls of different Asian descents [Table 1].

Sensitivity analysis

In addition, we have performed sensitivity analysis by omitting four studies in which the genotype distributions of BsmI, TaqI, FokI, and ApaI polymorphisms in the healthy controls significantly deviated from the HWE. However, the significance of pooled ORs not influenced by omitting those studies, indicating that the results was stable.

Publication bias

We have assessed the publication bias of the literature qualitatively by funnel plots and estimated quantitatively by Begg's and Egger's tests. The shape of the funnel plots no revealed evidence of obvious asymmetry. Moreover, the Egger's test was used to provide further statistical evidence of funnel plot symmetry. However, we did not find any evidence of publication bias of the literatures regarding the BsmI, TaqI, FokI, and ApaI polymorphisms and chronic periodontitis under the all genetic models [Figure 2a-d].

DISCUSSION

In this study, we examined the relationship between the polymorphism of widely investigated common

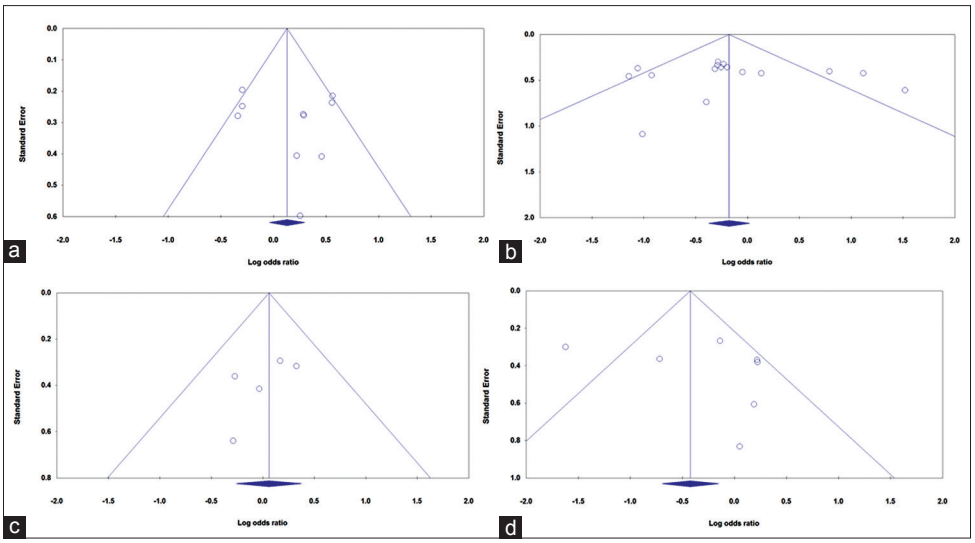

Figure 2: Begg's funnel plots of the Vitamin D receptor polymorphisms and chronic periodontitis susceptibility for publication bias test. (a) BsmI (allele model: A vs. G); (b) TaqI (heterozygote model: CT vs. TT); (c) FokI (dominant model: TT + TC vs. CC); and (d) ApaI (recessive model: TT vs. TG + GG).

polymorphisms in VDR gene and chronic periodontitis susceptibility. In 2010, Deng *et al*. performed a meta-analysis on VDR gene polymorphisms associations with periodontitis.[35] However, their results under cruise as their methodology in overall and subgroup analyses is not considerably correct. Thus, our main purpose of performing this meta-analysis was to improve statistical power and obtain more accurate quantitative results by increasing the sample size. Our meta-analysis indicates that BsmI polymorphism was not associated with increased chronic periodontitis risk when all eligible studies were pooled into the meta-analysis. In further stratified and sensitivity analyses, significantly increased chronic periodontitis risk was observed under the allele model in Caucasians for BsmI, but not in other ethnicities. Our results showed that carrying the BsmI minor allele may be a risk factor for chronic periodontitis in Caucasians. Similarly, some studies have shown that BsmI is associated with an increased risk of some autoimmune diseases including systemic lupus erythematosus[36] and diabetes type 1.[37] However, the functional significance of the BsmI polymorphism, which is located near the 3'-UTR region in intron 8, remains unclear. This polymorphism does not change the amino acid sequence of the encoded protein. However, it seems that BsmI may alter polyadenylation of the VDR mRNA transcript and thus affect gene expression through regulation of mRNA stability.[38]

In the present meta-analysis, we also failed to detect any association between TaqI and ApaI polymorphisms and chronic periodontitis susceptibility in all four genetic models, even by ethnicity. Our results were consistent with a previous meta-analysis on VDR gene polymorphisms with susceptibility to different conditions such as melanoma,[39] female reproductive cancers,[40] atopic dermatitis,[41] and polycystic ovary syndrome.[42] The reason for this lack of association could be explained with further haplotype studies. Some studies suggested that ApaI and TaqI polymorphisms are located at the 3'end of the VDR gene neighboring the 3'UTR region, which do not result in changes in the predicted amino acid sequence of the VDR.[43] In addition, our data suggest that FokI not significantly associated with chronic periodontitis susceptibility. The functional FokI polymorphism is the most important start codon polymorphism in VDR gene, which is located in exon 2 at the 5' coding region of the gene.[41-43]

Heterogeneity is an important problem when interpreting the results of a meta-analysis,[44-46] and identifying the sources of heterogeneity is one of the most important goals of meta-analysis.[47-49] In this study, significant between-study heterogeneity in the pooled analyses of all included studies was found for TaqI and ApaI polymorphisms. However, for these polymorphisms, the heterogeneity not disappeared fully after subgroup analysis by ethnicity and excluding the studies not in HWE.

We conducted the largest and most comprehensive quantitative meta-analysis of the relationship between VDR gene polymorphisms and chronic

periodontitis risk. However, the results of the present meta-analysis should also be interpreted within the context of its limitations. First, we have performed this meta-analysis based mainly on the results from published studies. Future analyses may include data from more unpublished datasets. Second, due to limited individual data, we did not conduct a more precise analysis on other covariates such as age, gender, and environmental factors. Third, compared with many large-sample genetic association studies, the sample size of included studies in our meta-analysis is relatively small, especially for FokI and ApaI, which may limit the statistical power of this meta-analysis. Finally, the current data support the multifactorial nature of periodontitis, and both genetic and environmental factors are involved in the pathogenesis of this disease. Therefore, our results may be affected by additional confounding factors, such as gender, age, environmental factors, and we could not take this into account in this meta-analysis because studies did not report the data.

CONCLUSION

We failed to detect any association between BsmI, TaqI, FokI, and ApaI polymorphisms in the VDR gene and chronic periodontitis susceptibility in the overall population. Moreover, due to limited sample size, more large-scale, multi-racial association studies are required to further clarify the genetic association between various VDR gene polymorphisms and risk of chronic periodontitis.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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