

RESEARCH ARTICLE

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# Effects of vitamin D receptor polymorphisms on urolithiasis risk: a meta-analysis

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## Abstract

**Background:** Several studies analyzed the associations of *Vitamin D receptor (VDR)* polymorphisms with urolithiasis risk in different ethnic groups. However, the results were inconclusive. To evaluate a more precise estimation of the relationship, a meta-analysis was performed.

**Methods:** Pubmed, EMBASE, Wanfang Database, China National Knowledge Infrastructure (CNKI) and Weipu Database were searched. Data were extracted independently by two investigators. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of associations.

**Results:** Twenty-three case-control studies were included in this meta-analysis. Significant associations between *Apal*, *BsmI*, *FokI*, and *TaqI* polymorphisms and urolithiasis risk were observed. However, sensitivity analyses for *BsmI* and *FokI* polymorphisms indicated that the results were not reliable and credible. In addition, there was a significant association of the *Apal-TaqI* haplotype with urolithiasis risk.

**Conclusions:** This meta-analysis suggested that *Apal* and *TaqI* polymorphisms in *VDR* gene were associated with urolithiasis risk.

**Keywords:** Urolithiasis, Vitamin D receptor, Polymorphism, Meta-analysis

## Background

Urolithiasis is one of the most prevalent uro-nephrologic disorders and affects approximately 10% of individuals in western countries [1]. The incidence of urolithiasis is increasing. For example, in the US the prevalence has risen from 3.2% to 5.2% in just over two decades from the mid-1970s to the mid-1990s [2]. Previous studies evidenced the importance of genes in this disease. Studies of kidney stone-forming twins demonstrated a higher concordance for kidney stones in monozygotic than in dizygotic twins [3]. Additionally, a family history was reported to increase the disease risk (2.57 times higher) in males [4]. Thus, it is important to identify the gene variants contributing to urolithiasis pathogenesis.

Recently, Elkoushy and coworkers found that patients with urolithiasis had a high prevalence of inadequate vitamin D [5]. Expression and nuclear activation of the Vitamin D receptor (VDR) are necessary for the effects

of vitamin D. Therefore, VDR was implicated in urolithiasis. In genetic hypercalciuric stone-forming (GHS) rats, Yao et al. [6] found that VDR mRNA levels were higher in kidney compared with wild-type controls. In addition, Favus et al. [7] showed that the level of VDR in peripheral blood monocytes was twofold greater in male calcium oxalate stone formers than in controls. Taken together, these results suggested that VDR may play an important role in the pathogenesis of urolithiasis.

The human *VDR* gene is located on chromosome 12q12-14. Four single nucleotide polymorphisms (SNPs) of the *VDR* gene have been widely studied [8]. *Apal*, *BsmI*, and *TaqI* are located between the 8 and 9 exons in the 3'-untranslated region (UTR), and shown to be in strong linkage disequilibrium (LD) [9]. Another SNP is the *FokI*, which is located at the translation starting codon. Many studies investigated the associations between these polymorphisms of *VDR* gene and the risk of urolithiasis [10-32]. However, the results were inconclusive. The inconsistent results were possibly due to the low statistical powers of individual studies. The method of meta-analysis could provide a quantitative approach

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for combining the results of various studies with the same topic. Therefore, we performed this meta-analysis to address the precise relationship between the *VDR* gene variants and urolithiasis risk.

## Methods

### Publication search

We performed a systematic search of Pubmed, EMBASE, Wanfang Database, China National Knowledge Infrastructure (CNKI) and Weipu Database to find relevant studies. The search terms were used as follows: (urolithiasis or kidney stone or kidney stone disease) and (Vitamin D receptor or *VDR*) and (polymorphism or mutation or variant). Last search was updated in October, 2012. No language restriction was imposed. The reference lists of searched articles and relevant reviews were all perused to find additional eligible studies.

### Inclusion and exclusion criteria

Two reviewers (Zhang and Nie) independently screened titles and abstracts of all studies for relevancy. Disagreements were resolved by discussion. Studies included in this meta-analysis based on the following selection criteria: (1) evaluation of the *Apal*, *BsmI*, *TaqI*, and *FokI* polymorphisms in *VDR* gene and urolithiasis risk, (2) using a case-control design, and (3) genotype distributions in both cases and controls should be available for estimating an odds ratio (OR) and 95% confidence interval (CI).

Studies were excluded if one of the following existed: (1) the *VDR* polymorphisms were not analyzed or the outcome was not urolithiasis risk, (2) not case-control studies, such as the design based on family or sibling pairs, (3) not reported genotype frequencies or number, (4) abstracts or reviews, and (5) non-clinical study. For overlapping studies, the one with the largest sample size was included.

### Data extraction

The full manuscripts of eligible studies were reviewed by two investigators (Zhang and Nie) independently. Any discrepancy was resolved by discussion or a third author (Jiang) would assess the articles. The following information was collected from each study: the first author's name, year of publication, original country, ethnicity, age group, hypercalciuria in the urolithiasis group, composition of stone, sample size, the polymorphisms in *VDR* gene, genotyping method, and genotype number in cases and controls. We contacted the corresponding authors if more data was needed.

### Quality assessment

The quality of the studies was assessed by two investigators (Zhang and Nie) independently. The predetermined

criteria were modified from a previous review [33]. These scores were based on traditional epidemiological considerations and genetic issues. Scores ranged from zero (lowest) to ten (highest). Disagreement was settled by discussion. Articles scoring  $< 5$  were defined as low quality, and those  $\geq 5$  were defined as high quality.

### Statistical analysis

When the data from at least three similar studies were available, meta-analysis was performed. The strength of the associations between the *Apal*, *BsmI*, *FokI*, and *TaqI* polymorphisms and urolithiasis risk was measured by ORs and 95% CIs. OR1, OR2, and OR3 were calculated for the genotypes: 1) AA vs. aa (OR1), aA vs. aa (OR2), and AA vs. aA (OR3) for the *Apal*, 2) bb vs. BB (OR1), bB vs. BB (OR2), and bb vs. bB (OR3) for the *BsmI*, 3) ff vs. FF (OR1), fF vs. FF (OR2), and ff vs. fF (OR3) for the *FokI*, and 4) tt vs. TT (OR1), tT vs. TT (OR2), and tt vs. tT (OR3) for the *TaqI*, respectively. The statistical significance of OR was analyzed by *Z* test. These pairwise differences were used to indicate the most appropriate genetic model as follows: if  $OR1 = OR3 \neq 1$  and  $OR2 = 1$ , then a recessive model was suggested; if  $OR1 = OR2 \neq 1$  and  $OR3 = 1$ , then a dominant model was suggested; if  $OR2 = 1/OR3 \neq 1$  and  $OR1 = 1$ , then a complete overdominant model was suggested; if  $OR1 > OR2 > 1$  and  $OR1 > OR3 > 1$  (or  $OR1 < OR2 < 1$  and  $OR1 < OR3 < 1$ ), then a codominant model was suggested [34,35]. Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except in the case of a codominant model) and to pool the results again. The pooled OR estimate of each study was calculated by the random-effects model.

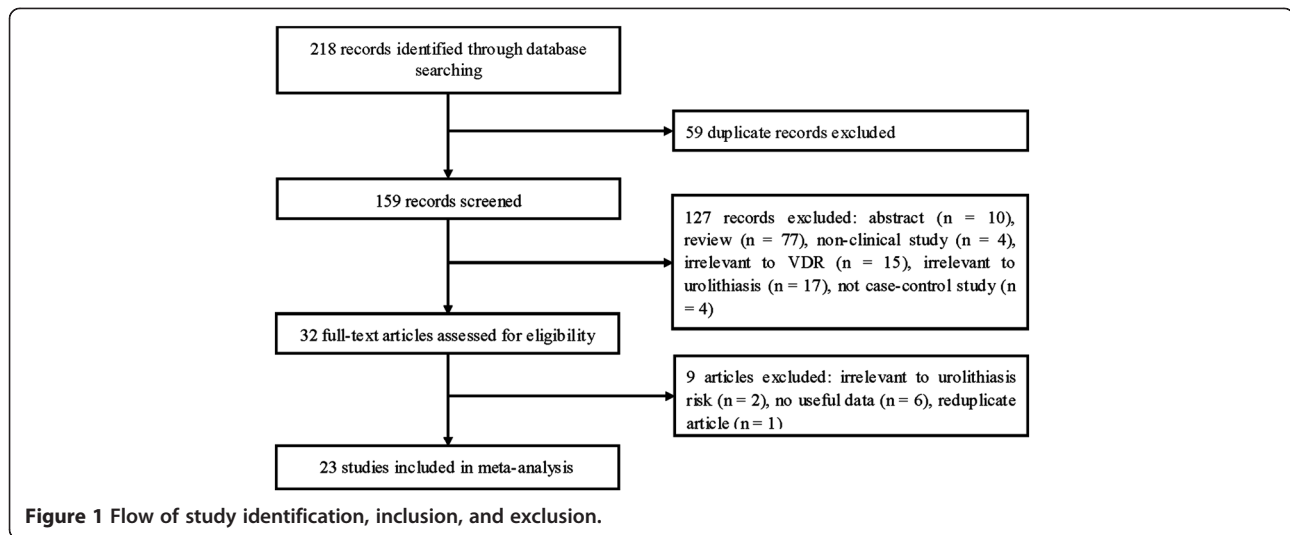
The between-study heterogeneity was assessed by the Chi square-test based Cochran *Q*-test and  $I^2$  test.  $I^2$  values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates. Departure from Hardy-Weinberg equilibrium (HWE) in controls was tested by the Chi-square test. Subgroup analyses were conducted by ethnicity, calciuria level, and age group. Sensitivity analyses were performed by excluding the studies not in HWE and the studies with low quality, respectively. Funnel plot was used to assess potential publication bias. Publication bias was also investigated statistically via Egger's test [36].

All statistical tests were performed by using STATA 11.0 software (Stata Corporation, College Station, TX). A *P* value  $< 0.05$  was considered statistically significant, except for test of heterogeneity where a level of 0.10 was used.

## Results

### Study characteristics

Figure 1 outlines our study selection process. A total of 218 articles were identified after an initial search. Fifty-



nine duplications were excluded. After reading the titles and abstracts, 127 articles were removed owing to abstracts, reviews, non-clinical studies, not case-control studies, and irrelevant to urolithiasis or *VDR* polymorphisms. After reading the full texts of the remaining 32 articles, 9 articles were excluded due to irrelevant to urolithiasis risk, no useful data, and reduplicate study. Finally, a total of 23 case-control studies met our inclusion criteria. There were 11 studies on *Apal*, 8 on *BsmI*, 14 on *FokI*, 13 studies on *TaqI*. Four studies reported the haplotype of *Apal* and *TaqI* polymorphisms. There were 14 studies of Asians and 9 studies of Caucasians. Seventeen studies were performed in adults, 3 in children, and 1 did not offer detailed information. Three studies only included patients with hypercalciuria, 6 studies included hypercalciuria patients partly and the data for these patients could be extracted, and 14 studies did not report detailed information. Quality scores for the each study ranged from 3 to 6. The characteristics of each study are presented in Table 1.

## Quantitative data synthesis

### *VDR Apal* polymorphism

Eleven studies determined the association between *Apal* polymorphism and urolithiasis risk. Total sample sizes in urolithiasis and control groups were 1584 and 1853. The estimated OR1, OR2 and OR3 were 1.47, 1.30, and 1.04, respectively (Table 2). These estimates suggested a dominant genetic model, and therefore AA and aA were combined and compared with aa. As shown in Figure 2, the pooled OR was 1.34 (95% CI 1.11 – 1.60,  $P = 0.002$ ). In the subgroup analysis by ethnicity, a significant association was found among Asians (OR = 1.43, 95% 1.16 – 1.75,  $P < 0.001$ ) but not among Caucasians (OR = 1.08, 95% 0.74 – 1.57,  $P = 0.69$ ). Subgroup analysis was also performed according to the calciuria level. However, no

significant increased risk of urolithiasis was found among hypercalciuric patients (OR = 1.24, 95% CI 0.86 – 1.81,  $P = 0.25$ ) (Table 2). In the subgroup analysis by age group, a significant association was observed among adults (OR = 1.30, 95% 1.04 – 1.62,  $P = 0.02$ ). Sensitivity analysis was performed by excluding the studies that did not show HWE. The result was statistically significant (OR = 1.30, 95% CI 1.04 – 1.62,  $P = 0.02$ ). Sensitivity analysis was also performed by excluding the low quality studies. The result was similar (OR = 1.34, 95% CI 1.09 – 1.66,  $P = 0.006$ ). The shape of the funnel plot showed symmetric (Figure 3). Egger's test did not indicate significant publication bias ( $P = 0.914$ ).

### *VDR BsmI* polymorphism

Eight studies (1210 cases and 1160 controls) that identified the association between *VDR BsmI* polymorphism and urolithiasis risk were included in this meta-analysis. The estimated OR1, OR2 and OR3 were 1.79, 1.85, and 0.96, respectively (Table 2). These estimates suggested a dominant genetic model. The pooled OR was 1.81 (95% CI 1.03 – 3.17,  $P = 0.04$ ) (Figure 4). In the subgroup analysis by ethnicity, a marginally significant association was found among Caucasians (OR = 2.43, 95% CI 1.02 – 5.80,  $P = 0.05$ ) but not among Asians (OR 1.21, 95% CI 0.67 – 2.32,  $P = 0.49$ ) (Table 2). In addition, subgroup analysis in hypercalciuric patients showed significant increased risk of urolithiasis (OR 2.43, 95% CI 1.36 – 4.35,  $P = 0.003$ ). In the stratified analysis by ethnicity, no significant association was found among adults (OR 0.80, 95% CI 0.96 – 3.38,  $P = 0.07$ ). However, sensitivity analyses conducted by excluding the studies not in HWE or low quality studies did not find the significant association between *VDR BsmI* polymorphism and urolithiasis risk (Table 2). No publication bias was detected by funnel plot (Figure 5) and Egger's test ( $P = 0.461$ ).

**Table 1 Characteristics of the case-control studies included in meta-analysis**

First author	Year	Country	Ethnicity	Age group	Hypercalciuria in case group	Composition	Case (n)	Control (n)	VDR polymorphisms (HWE)	Genotyping method	Quality score
Ruggiero [10]	1999	Italy	Caucasian	Adult	Mixed*	NA	27	150	<i>BsmI</i> (No)	PCR-RFLP	4
Jackman [11]	1999	USA	Caucasian	NA	All	Calcium	17	37	<i>TaqI</i> (No)	PCR-RFLP	3
Chen a [12]	2001	China	Asian	Adult	NA	Calcium	124	90	<i>BsmI</i> (No)	PCR-RFLP	4
Chen b [13]	2001	China	Asian	Adult	NA	Calcium	146	90	<i>FokI</i> (Yes)	PCR-RFLP	4
Nishijima [14]	2002	Japan	Asian	Adult	NA	Calcium	83	83	<i>Apal</i> (Yes), <i>TaqI</i> (Yes)	PCR-RFLP	5
Mossetti [15]	2003	Italy	Caucasian	Adult	NA	Calcium	220	114	<i>BsmI</i> (Yes), <i>TaqI</i> (No)	PCR-RFLP	5
Ozkaya [16]	2003	Turkey	Caucasian	Children	All	Calcium	64	90	<i>Apal</i> (No), <i>BsmI</i> (Yes), <i>TaqI</i> (Yes)	PCR-RFLP	4
Wang a [17]	2003	China	Asian	Adult	Mixed*	Calcium	150	80	<i>Apal</i> (Yes), <i>FokI</i> (Yes), <i>TaqI</i> (Yes)	PCR-RFLP	3
Relan [18]	2004	India	Asian	Adult	Mixed*	Calcium	150	100	<i>BsmI</i> (No), <i>FokI</i> (No)	PCR-RFLP	3
Rendina [19]	2004	Italy	Caucasian	Adult	All	Calcium	159	124	<i>Apal</i> (Yes), <i>FokI</i> (Yes)	PCR-RFLP	6
Hu [20]	2004	China	Asian	Adult	Mixed*	Calcium	186	90	<i>Apal</i> (Yes), <i>FokI</i> (Yes), <i>TaqI</i> (Yes)	PCR-RFLP	5
Bid a [21]	2005	India	Asian	Adult	Mixed*	Calcium	138	166	<i>FokI</i> (No)	PCR-RFLP	4
Bid b [22]	2005	India	Asian	Children	NA	Calcium	50	60	<i>FokI</i> (Yes)	PCR-RFLP	5
Gunes [23]	2006	Turkey	Caucasian	Adult	NA	Calcium	110	150	<i>Apal</i> (Yes), <i>BsmI</i> (Yes), <i>TaqI</i> (Yes)	PCR-RFLP	6
Liu [24]	2007	China	Asian	Adult	NA	Calcium	235	231	<i>FokI</i> (Yes)	PCR-RFLP	6
Moyano [25]	2007	Spain	Caucasian	Adult	NA	Calcium	51	21	<i>Apal</i> (Yes), <i>BsmI</i> (Yes), <i>TaqI</i> (Yes)	PCR-RFLP	3
Seyhan [26]	2007	Turkey	Caucasian	Children	Mixed*	Calcium	80	40	<i>TaqI</i> (No)	PCR-RFLP	4
Wang b [27]	2009	China	Asian	Mixed	NA	Calcium	90	90	<i>Apal</i> (No), <i>FokI</i> (No)	PCR-RFLP	5
Mittal [28]	2010	India	Asian	Adult	NA	NA	125	150	<i>Apal</i> (Yes), <i>FokI</i> (No), <i>TaqI</i> (No)	PCR-RFLP	5
Seo [29]	2010	Korea	Asian	Mixed	NA	Calcium	102	535	<i>Apal</i> (No), <i>FokI</i> (No), <i>TaqI</i> (No)	PCR-RFLP	5
Basiri [30]	2012	Iran	Caucasian	Adult	NA	Calcium	106	109	<i>FokI</i> (No), <i>TaqI</i> (No)	PCR-SSCP	5
Wang c [31]	2012	China	Asian	Adult	NA	Calcium	464	450	<i>Apal</i> (Yes), <i>BsmI</i> (Yes), <i>FokI</i> (Yes), <i>TaqI</i> (Yes)	PCR-RFLP	6
Ruan [32]	2012	China	Asian	Adult	NA	Calcium	169	156	<i>FokI</i> (No)	PCR-RFLP	4

\*Data for hypercalciuria patients could be extracted.

HWE, Hardy-Weinberg equilibrium; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSCP, single-strand conformational polymorphism; NA, not available.

### VDR *FokI* polymorphism

For the *VDR FokI* polymorphism, fourteen studies including 2266 cases and 2418 controls were included in this meta-analysis. OR1, OR2, and OR3 were 1.59, 1.38, and 1.04, respectively. These estimates suggested a dominant genetic model. Therefore, the original grouping was collapsed, and ff and fF were combined, in accordance with a dominant model, into a f carrier group, the latter of which was compared with the FF genotype group. The pooled OR was 1.48 (95% CI 1.03 – 2.12,  $P = 0.03$ ) (Figure 6). In the subgroup analysis by ethnicity, no significant association was found among Asians (OR = 1.32, 95% CI 0.94 – 1.86,  $P = 0.11$ ) (Table 2). In the subgroup analysis by the calciuria level, there was still no significant association

between *VDR FokI* polymorphism and urolithiasis risk in patients with hypercalciuria (OR = 1.15, 95% CI 0.81 – 1.63,  $P = 0.43$ ) (Table 2). Statistically significant increased urolithiasis risk was observed among adults group (OR = 1.71, 95% CI 1.14 – 2.56,  $P = 0.009$ ). Sensitivity analyses found that the significant result was altered when the low quality studies or studies with Hardy-Weinberg disequilibrium were omitted (Table 2). The shape of the funnel plot seemed symmetrical (Figure 7). Egger's test did not show evidence of publication bias ( $P = 0.081$ ).

### VDR *TaqI* polymorphism

Thirteen studies including 1744 patients and 1944 controls addressed the association between *VDR TaqI*

**Table 2 Summary of different comparative results**

Polymorphisms	Study	Sample size		No. of studies	Test of association			Model	Heterogeneity		
		Case	Control		OR (95% CI)	Z	P Value		$\chi^2$	P Value	I <sup>2</sup> (%)
<i>Apal</i>											
AA vs. aa	Overall	846	1048	11	1.47 (1.11-1.94)	2.66	0.008	R	13.03	0.220	23.0
aA vs. aa	Overall	1059	1368	11	1.30 (1.06-1.60)	2.54	0.010	R	10.98	0.360	9.0
AA vs. aA	Overall	1263	1290	11	1.04 (0.76-1.43)	0.25	0.810	R	26.31	0.003	62.0
AA + aA vs. aa	Overall	1584	1853	11	1.34 (1.11-1.60)	3.12	0.002	R	7.49	0.680	0.0
AA + aA vs. aa	Asian	1200	1468	7	1.43 (1.16-1.75)	4.57	<0.001	R	4.57	0.600	0.0
AA + aA vs. aa	Caucasian	384	385	4	1.08 (0.74-1.57)	0.40	0.690	R	1.32	0.730	0.0
AA + aA vs. aa	Hypercalciuria	295	262	4	1.24 (0.86-1.81)	1.15	0.250	R	3.10	0.380	3.0
AA + aA vs. aa	Adult	1328	1148	8	1.30 (1.04-1.62)	2.33	0.020	R	3.99	0.780	0.0
AA + aA vs. aa	HWE	1328	1148	8	1.30 (1.04-1.62)	2.33	0.020	R	3.99	0.780	0.0
AA + aA vs. aa	High quality	1319	1662	8	1.34 (1.09-1.66)	2.75	0.006	R	7.41	0.390	6.0
<i>BsmI</i>											
bb vs. BB	Overall	841	855	8	1.79 (0.98-3.26)	1.89	0.060	R	18.93	0.008	63.0
bB vs. BB	Overall	611	609	8	1.85 (1.03-3.32)	2.05	0.040	R	21.94	0.003	68.0
bb vs. bB	Overall	966	856	8	0.96 (0.77-1.20)	0.33	0.740	R	5.01	0.660	0.0
bb + bB vs. BB	Overall	1210	1160	8	1.81 (1.03-3.17)	2.07	0.040	R	23.82	0.001	71.0
bb + bB vs. BB	Asian	738	640	3	1.21 (0.67-2.32)	0.69	0.490	R	3.10	0.210	36.0
bb + bB vs. BB	Caucasian	472	520	5	2.43 (1.02-5.80)	2.00	0.050	R	19.52	<0.001	80.0
bb + bB vs. BB	Hypercalciuria	123	340	3	2.43 (1.36-4.35)	2.99	0.003	R	1.99	0.370	0.0
bb + bB vs. BB	Adult	1146	1070	7	1.80 (0.96-3.38)	1.83	0.070	R	23.65	<0.001	75.0
bb + bB vs. BB	HWE	909	820	5	1.36 (0.87-2.13)	1.35	0.180	R	4.90	0.300	18.0
bb + bB vs. BB	High quality	794	709	3	1.15 (0.75-1.72)	0.66	0.510	R	1.01	0.600	0.0
<i>FokI</i>											
ff vs. FF	Overall	1144	1243	14	1.59 (1.08-2.35)	2.34	0.020	R	47.26	<0.001	72.0
fF vs. FF	Overall	1647	1809	14	1.38 (0.96-2.00)	1.72	0.090	R	64.13	<0.001	80.0
ff vs. fF	Overall	1741	1804	14	1.04 (0.74-1.45)	0.22	0.830	R	56.68	<0.001	77.0
ff + fF vs. FF	Overall	2266	2418	14	1.48 (1.03-2.12)	2.12	0.030	R	68.26	<0.001	81.0
ff + fF vs. FF	Asian	2005	2188	12	1.32 (0.94-1.86)	1.62	0.110	R	44.62	<0.001	75.0
ff + fF vs. FF	Hypercalciuria	324	560	5	1.15 (0.81-1.63)	0.79	0.430	R	1.42	0.840	0.0
ff + fF vs. FF	Adult	2024	1743	11	1.71 (1.14-2.56)	2.61	0.009	R	59.01	<0.001	83.0
ff + fF vs. FF	HWE	1390	1125	7	1.05 (0.83-1.33)	0.39	0.700	R	8.54	0.200	30.0
ff + fF vs. FF	High quality	1513	1348	7	1.34 (0.83-2.16)	1.19	0.230	R	53.59	<0.001	85.0
<i>TaqI</i>											
tt vs. TT	Overall	1144	1478	13	1.24 (0.92-1.68)	1.40	0.160	R	12.19	0.430	2.0
tT vs. TT	Overall	1558	1786	13	1.33 (1.04-1.70)	2.28	0.020	R	21.41	0.040	44.0
tt vs. tT	Overall	806	624	13	0.92 (0.61-1.38)	0.40	0.690	R	21.56	0.040	44.0
tt + tT vs. TT	Overall	1744	1944	13	1.30 (1.08-1.55)	2.79	0.005	R	13.54	0.330	11.0
tt + tT vs. TT	Asian	1110	1386	6	1.39 (1.11-1.73)	2.87	0.004	R	4.32	0.500	0.0
tt + tT vs. TT	Caucasian	644	558	7	1.21 (0.84-1.72)	1.02	0.310	R	10.06	0.120	40.0
tt + tT vs. TT	Hypercalciuria	176	183	5	1.56 (1.06-2.31)	2.24	0.030	R	2.47	0.650	0.0
tt + tT vs. TT	Adult	1481	1244	9	1.34 (1.05-1.71)	2.35	0.020	R	12.71	0.120	37.0
tt + tT vs. TT	HWE	1098	964	7	1.36 (1.07-1.77)	2.51	0.010	R	7.44	0.280	19.0
tt + tT vs. TT	High quality	1392	1676	8	1.27 (1.05-1.54)	2.43	0.010	R	9.23	0.240	24.0

**Table 2 Summary of different comparative results (Continued)**

<i>Apal-Taql</i> haplotype												
At vs. aT	Overall	830	1207	4	1.35 (1.09-1.68)	2.71	0.007	R	2.91	0.410	0.0	
At vs. aT	Asian	644	961	3	1.53 (1.17-2.00)	3.14	0.002	R	0.35	0.840	0.0	
At vs. aT	Adult	752	806	3	1.36 (1.03-1.80)	2.16	0.030	R	2.90	0.230	31.0	

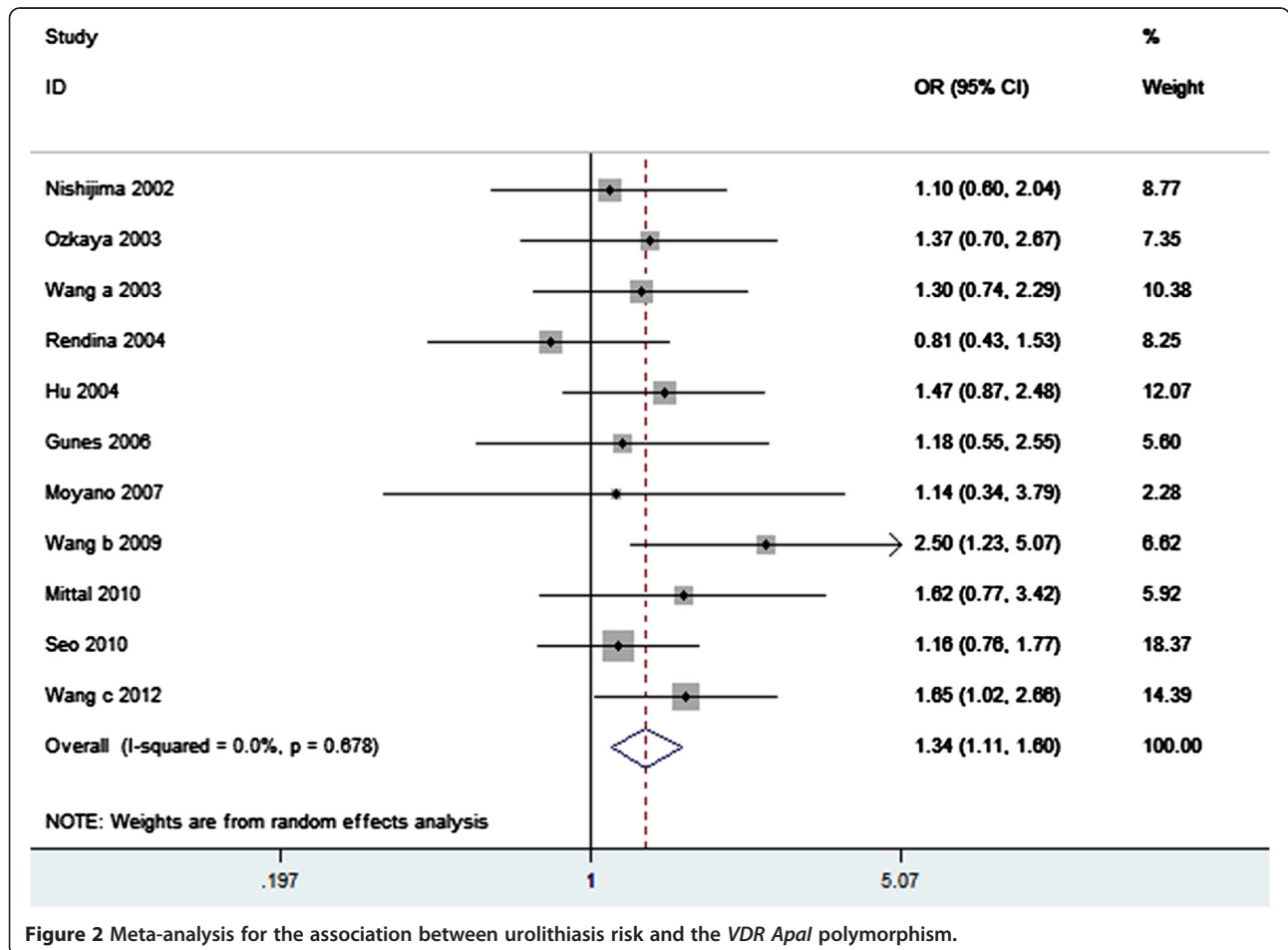
vs., versus; HWE, Hardy-Weinberg equilibrium; R, random-effects model.

polymorphism and urolithiasis. The estimated OR1, OR2 and OR3 were 1.24, 1.33, and 0.92, respectively. These pooling estimates suggested a dominant genetic model. The pooled OR in the dominant genetic model was 1.30 (95% CI 1.08 – 1.55,  $P = 0.005$ ) (Figure 8). In the stratified analysis, statistically significant increased urolithiasis risk was observed among Asians (OR = 1.39, 95% CI 1.11 – 1.73,  $P = 0.004$ ) but not Caucasians (OR = 1.21, 95% CI 0.84 – 1.72,  $P = 0.31$ ). Furthermore, patients with hypercalciuria had a significant increase of the risk of developing urolithiasis (OR = 1.56, 95% CI 1.06 – 2.31,  $P = 0.03$ ). In addition, significantly increased urolithiasis risks were found among adults (OR = 1.34, 95% CI 1.05 – 1.71,  $P = 0.02$ ). Sensitivity analysis did not change the

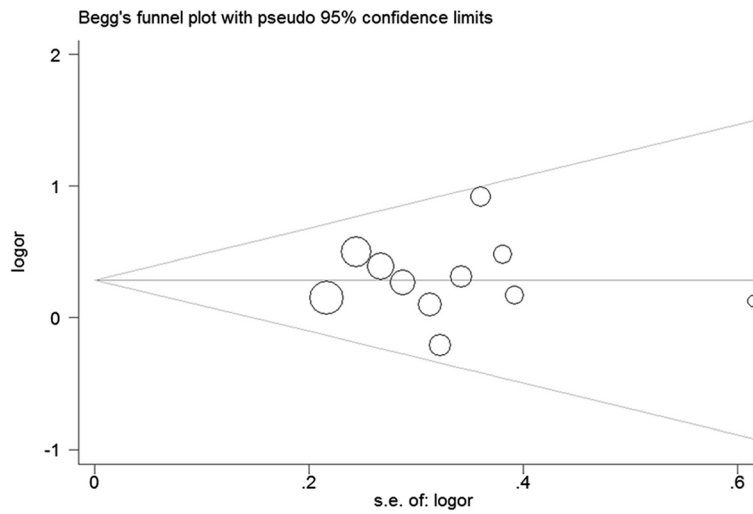
result (Table 2). The funnel plot appeared to be symmetrical (Figure 9). Egger's test were performed to estimate the publication bias. Publication bias was not observed ( $P = 0.122$ ).

**VDR *Apal-Taql* haplotype**

In 4 out of 23 studies, the role of *VDR Apal-Taql* haplotype in urolithiasis risk was analyzed. The sample sizes in case group and control group were 830 and 1207, respectively. Carling et al. [37] reported that the At haplotype displayed higher levels of mRNA expression than aT haplotype. Thus, the effect of these two haplotypes on the risk of urolithiasis was evaluated in this meta-analysis. As shown in Figure 10, the pooling



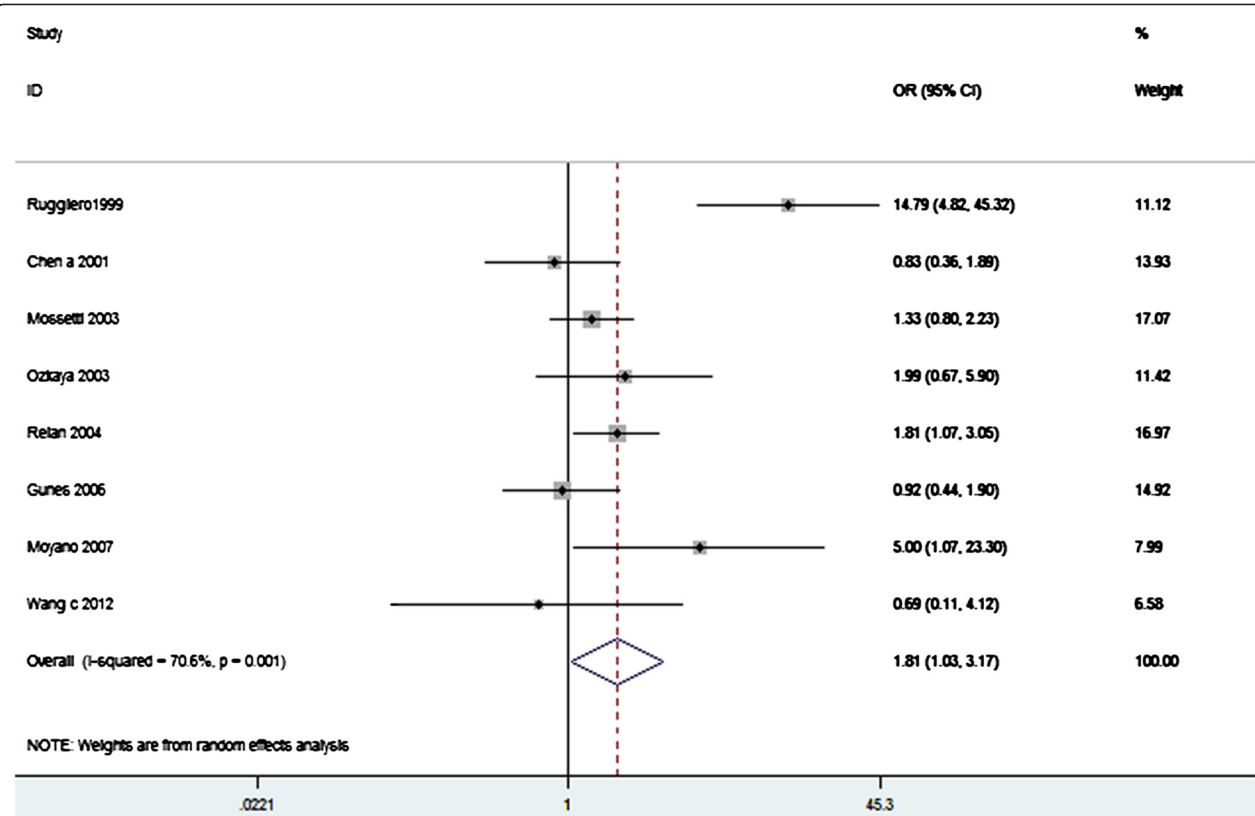
**Figure 2** Meta-analysis for the association between urolithiasis risk and the *VDR Apal* polymorphism.



**Figure 3** Funnel plot for publication bias in selection of studies on the VDR *Apal* polymorphism.

estimate showed a significant increased risk of developing urolithiasis in subjects with the At haplotype (OR = 1.35, 95% CI 1.09 – 1.68,  $P = 0.007$ ). In the subgroup analysis by ethnicity, a significant association was found among Asians (OR = 1.53, 95% CI 1.17 –

2.00,  $P = 0.002$ ). In the stratified analysis of age group, we also found a significant association (OR = 1.36, 95% CI 1.03 – 1.80,  $P = 0.03$ ). Symmetrical funnel plot was obtained (Figure 11). Publication bias was not observed ( $P = 0.887$ ).



**Figure 4** Meta-analysis for the association between urolithiasis risk and the VDR *BsmI* polymorphism.

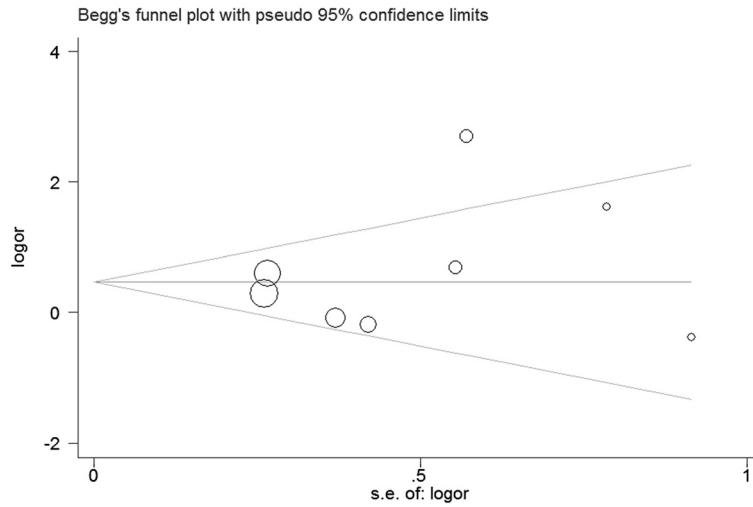


Figure 5 Funnel plot for publication bias in selection of studies on the *VDR BsmI* polymorphism polymorphism.

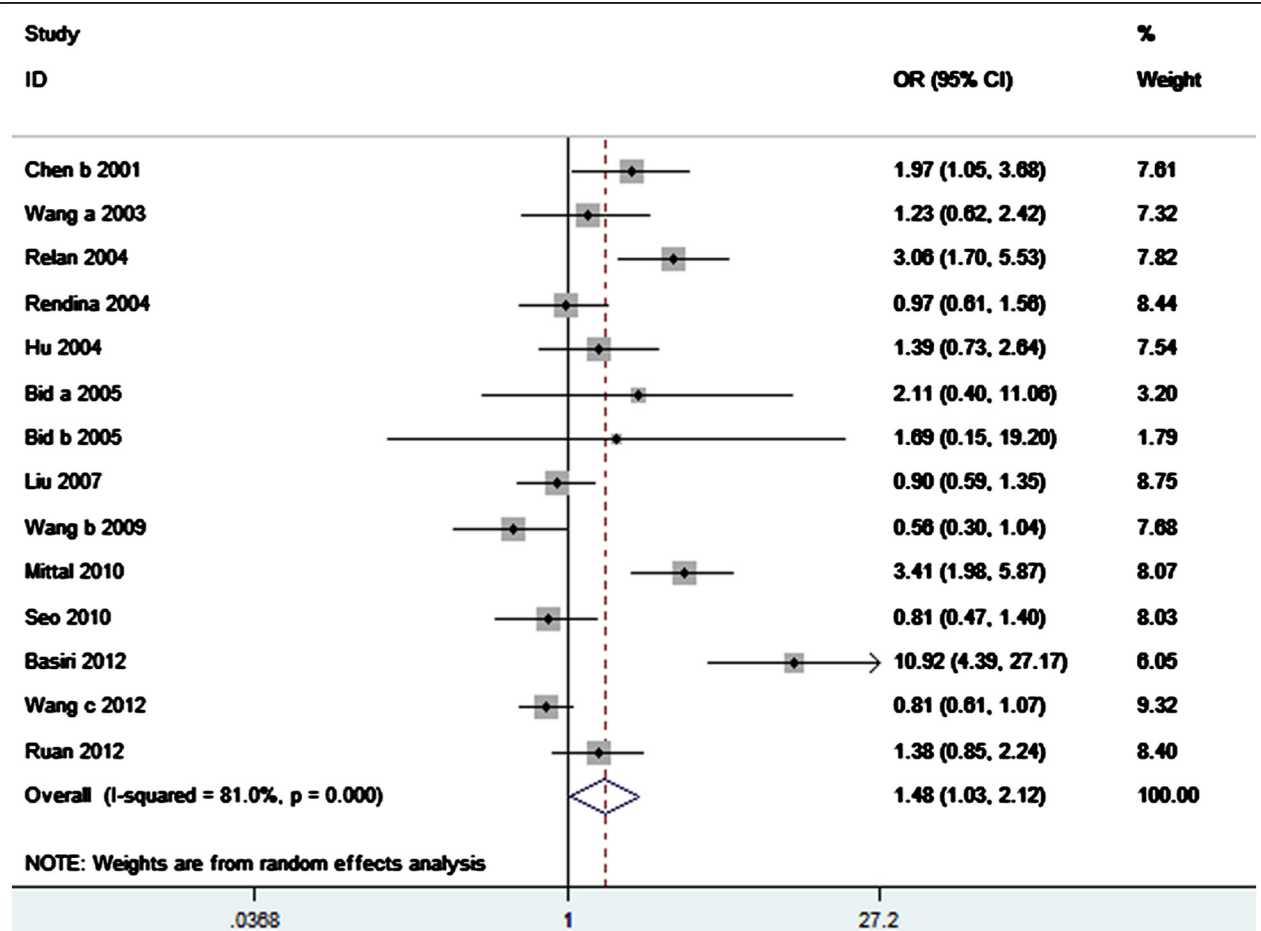


Figure 6 Meta-analysis for the association between urolithiasis risk and the *VDR FokI* polymorphism.



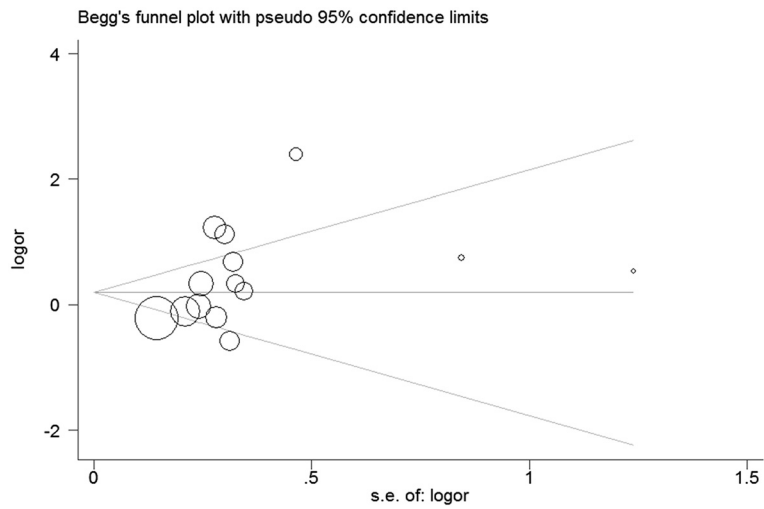


Figure 7 Funnel plot for publication bias in selection of studies on the *VDR FokI* polymorphism.

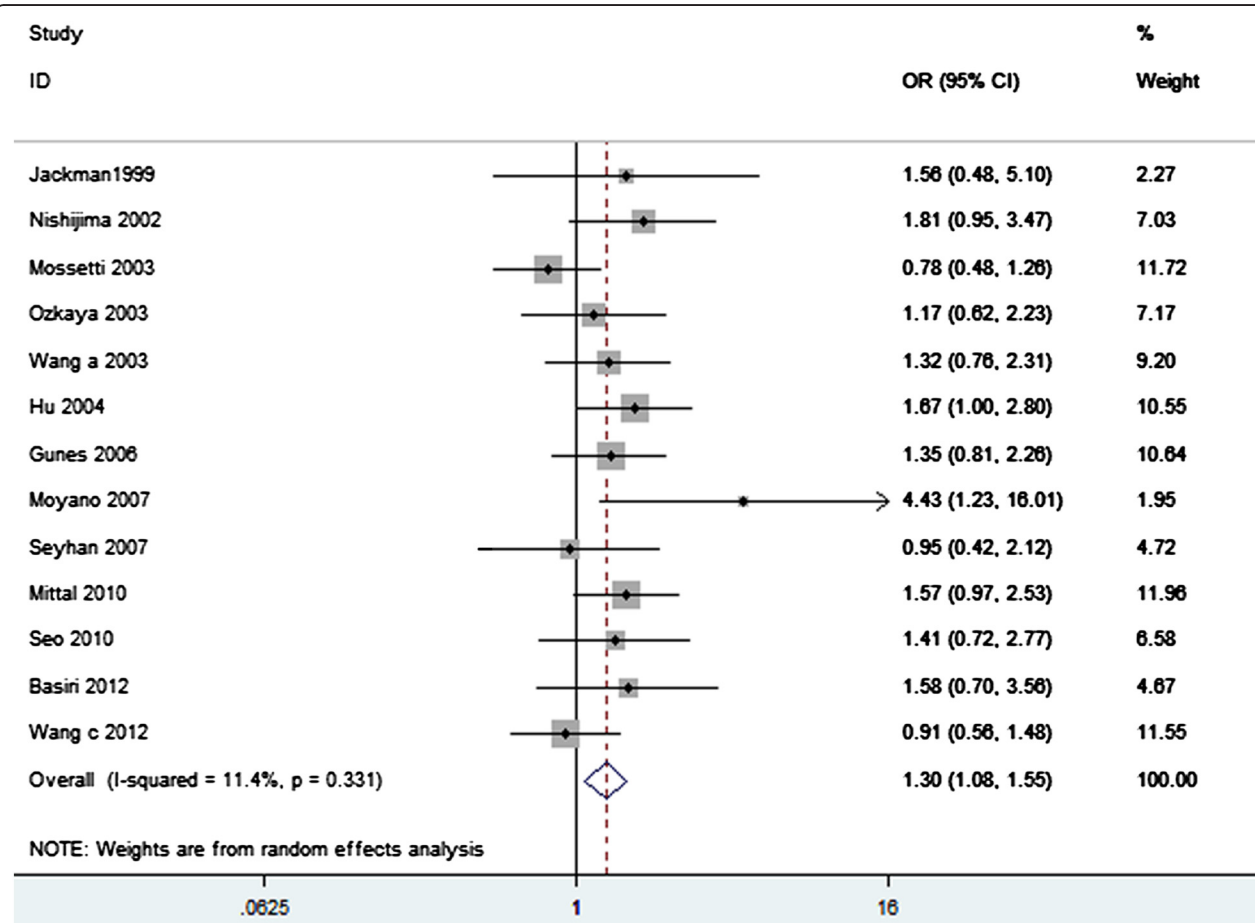
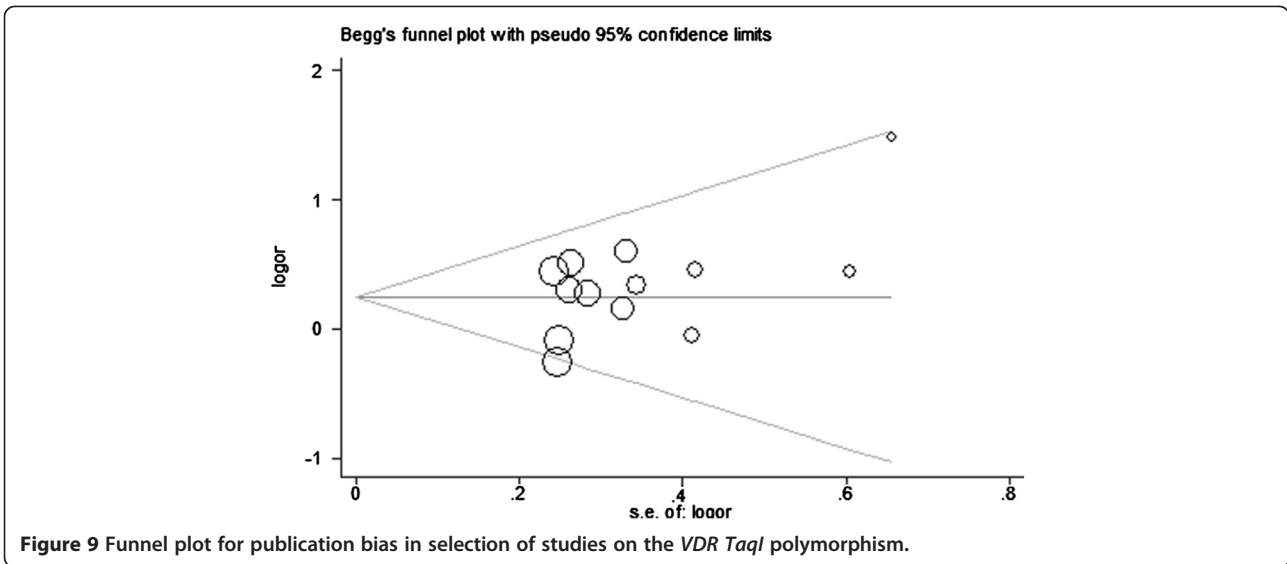


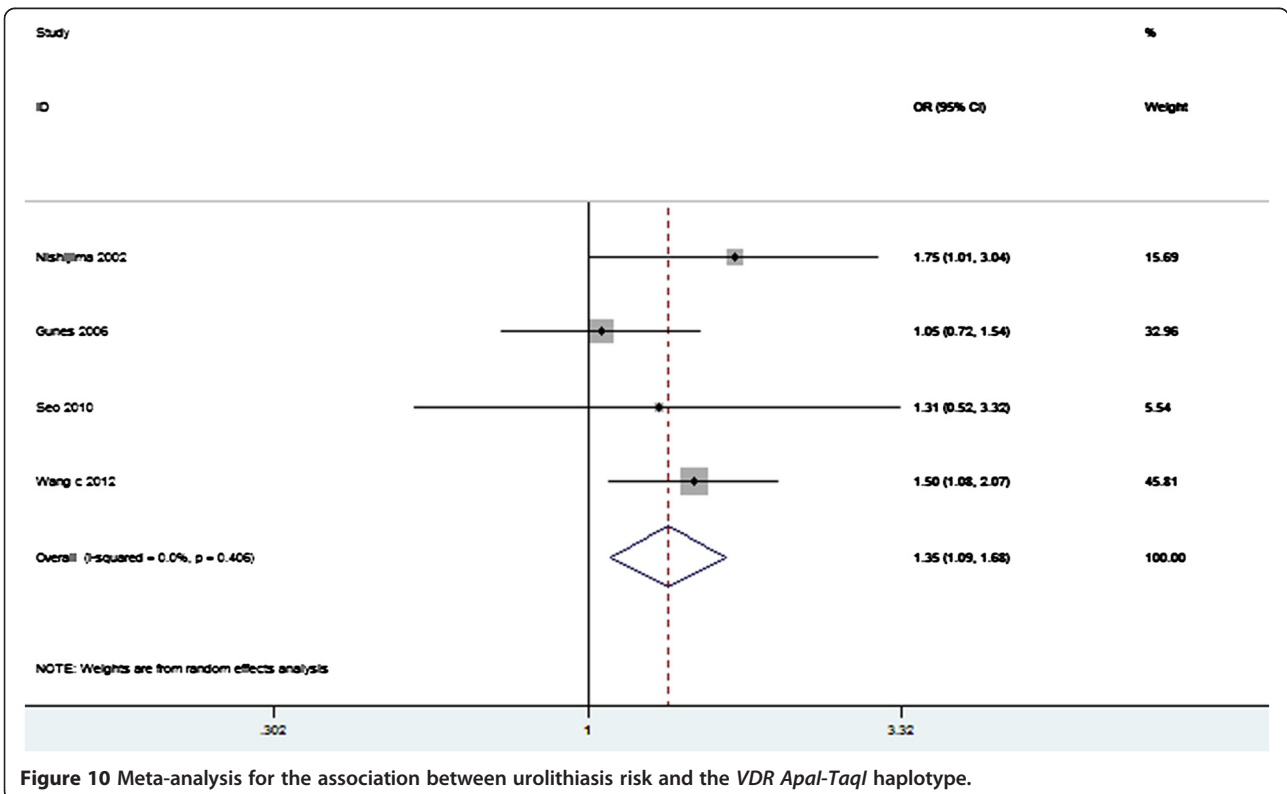
Figure 8 Meta-analysis for the association between urolithiasis risk and the *VDR TaqI* polymorphism.

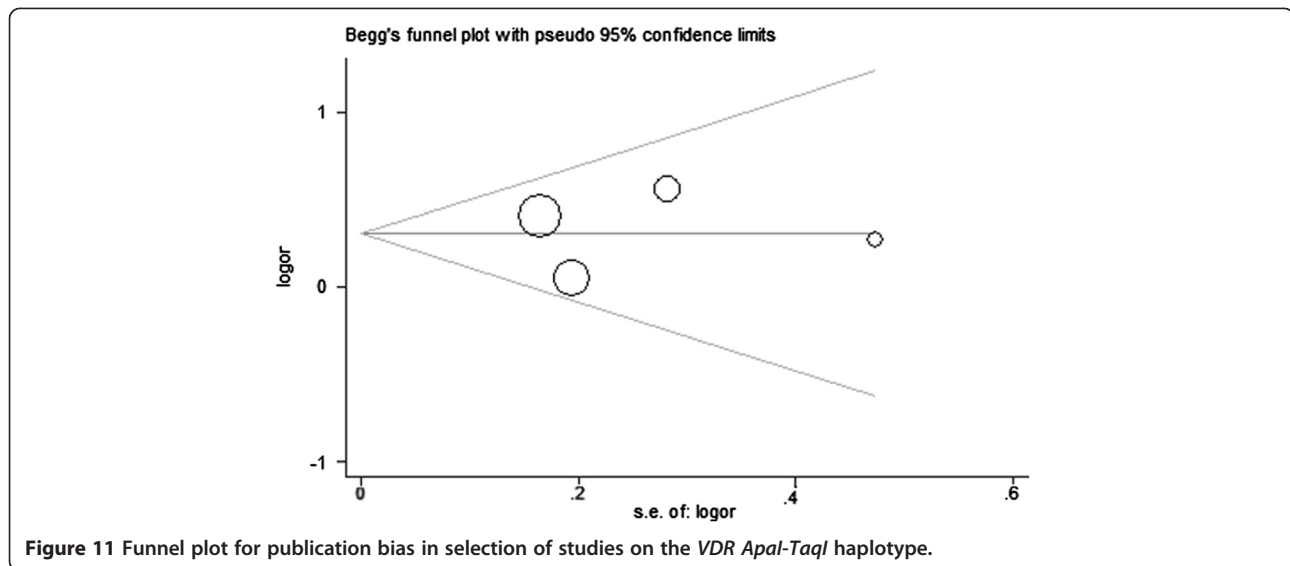


### Discussion

This present meta-analysis systematic investigated the associations between *VDR* polymorphisms and urolithiasis risk. We found that *Apal* polymorphism was a risk factor for developing urolithiasis. This result indicated that the carriers of the AA or Aa genotype had a 34% increased urolithiasis risk compared to those individuals with the aa genotype. Sensitivity analysis did not change this result, suggesting the solidity of our result. In the

stratified analysis by ethnicity, the significant association was found in Asian population but not in Caucasian population. In addition, *BsmI* and *FokI* polymorphisms were also significantly associated with urolithiasis risk in the overall population. However, results from sensitivity analyses suggested that these results were not statistically robust. Therefore, these results should be interpreted with caution and more studies are needed to evaluate the effect of *BsmI* and *FokI* polymorphisms on urolithiasis risk.





**Figure 11** Funnel plot for publication bias in selection of studies on the *VDR ApaI-TaqI* haplotype.

Specifically, we noted that hypercalciuric patients who harbored b allele may have increased urolithiasis risk. As for the *TaqI* polymorphism, a significant association was observed between this polymorphism and the risk of urolithiasis. Sensitivity analyses further strengthened the validity of this result. When subgroup analysis was conducted according to the ethnicity, the significant association was showed in Asians and lack of a significant association was detected in Caucasian population. In the hypercalciuria subgroup analysis, a 56% increased risk of urolithiasis was found in patients with hypercalciuria. Collectively, these results suggested that *VDR BsmI* and *TaqI* polymorphisms may play unique roles in the etiology of hypercalciuric urolithiasis. However, because the number of studies included in the hypercalciuria subgroup analyses was small, the results lacked sufficient reliability to confirm these associations in a definitive manner. Thus, future studies with larger sample sizes are needed to confirm our results. Furthermore, we assessed the association between the haplotypes of the *ApaI* and *TaqI* polymorphisms and urolithiasis risk. The result from this meta-analysis suggested that At haplotype may play a role in urolithiasis susceptibility, especially in Asians. Taken together, our results exhibited significant associations between *ApaI* and *TaqI* polymorphisms and urolithiasis risk in Asian population but not in Caucasian population. There are at least four reasons to explain the ethnic difference. First, the number of Caucasian patients was small. There were only 384 and 644 Caucasian patients for these two polymorphisms, respectively. It was therefore possible that the observed ethnic difference was due to chance. More studies with Caucasian population are required to validate the effect of ethnic differences. Second, higher heterogeneity was observed in the Caucasians subgroup ( $I^2 = 40\%$ ) but not in the Asians subgroup ( $I^2 = 0\%$ ) in *TaqI*

polymorphism. This may distort the result. Third, urolithiasis is a complex disease. Both genetic and environmental factors could affect the risk of urolithiasis in different populations. It is possible that different urolithiasis risks in Asians and Caucasians were due to exposure to various environmental factors. To date, there was no reported study which was performed to assess the effect of *VDR*-environment interactions on urolithiasis risk in different ethnicities and regions. Therefore, epidemiologic studies should be designed to examine these associations in the future. Fourth, ethnic difference in the *VDR* gene allele frequencies may also result in this difference. For example, the A allele of the *ApaI*, occurred with lower frequency in Caucasians when compared to Asians, while the t allele of the *TaqI* had a higher frequency in Asians compared to Caucasians [38]. We also performed subgroup analyses by age group. There were still significant associations in the adults group except in *BsmI* polymorphism. These results indicated that these polymorphisms were significantly associated with increased urolithiasis risk in adults. We did not evaluate the associations between *VDR* polymorphisms and urolithiasis risk in children due to insufficient data. More studies using children population are needed to determine the associations between *VDR* polymorphisms and urolithiasis risk.

A considerable weight of evidence supporting a role for *VDR* in urolithiasis was derived from GHS rats. Experimental studies using GHS rats showed increased levels of *VDR* in intestine, bones and kidneys [6,39]. Moreover, Karnauskas et al. [40] found that prolongation of *VDR* half-life increased *VDR* tissue levels and mediated *VDR*-regulated genes that led to hypercalciuria. Recently, using microRNA targeting *VDR*, Xi and colleagues silenced the *VDR* gene in the kidneys of GHS rats [41]. They demonstrated *VDR* knockdown in the kidney can

upregulate the expression of transient receptor potential vanilloid receptor subtype 5 (TRPV5) in GHS rats [41]. Previous study found that mice lacking TRPV5 exhibited reduced calcium reabsorption, which caused severe hypercalciuria [42]. In addition, hypercalciuria increased the risk for calcium oxalate nephrolithiasis and occurred in up to 50% of nephrolithiasis patients [43,44]. Therefore, high VDR level might contribute to the development of urolithiasis. VDR was one of the most studied candidate genes for urolithiasis. Carling et al. [37] showed that the individuals exhibiting the BB, AA, or tt genotypes had significantly higher VDR levels than those with homozygous for the b, a, or T alleles. They also found those exhibiting the baT haplotype demonstrated a relative lower VDR mRNA level than subjects with non-baT haplotype [37]. Furthermore, Yamagata et al. [45] showed the VDR mRNA levels of allele t were significantly higher than those of allele T in peripheral blood mononuclear cell (PBMC). Thus, it is biologically plausible that subjects with the B, A, or t alleles may have increased risk of urolithiasis. Our findings supported this speculation and the At haplotype carriers had increased urolithiasis risk than the aT haplotype carriers. However, we found that b allele carriers, but not B allele carriers, were associated with urolithiasis, although this result was not robust. Notably, hypercalciuric patients with b allele were seemed to have higher urolithiasis risk in the subgroup analysis. This result agreed with the report of Ferreira et al. [46], who also found that bb homozygous for VDR polymorphism was overrepresented in hypercalciuric stone formers. Additionally, Relan and co-authors reported that subjects with the bb genotype exhibited a higher urinary calcium excretion than the BB genotype [18]. Ruggiero et al. [10] found the similar phenomenon. The altered function of the VDR gene for the *BsmI* polymorphism may be associated with higher urinary calcium excretion. Hypercalciuria was a risk factor of urolithiasis. It was thus possible that b allele carriers may have higher urolithiasis risk than B allele carriers. As for the *FokI* polymorphism, Jurutka et al. [47] suggested that F variant possessed elevated transcriptional activity compared with the f variant. However, there was no difference between these two variants on the VDR expression [47]. Results from our study suggested that there was a significant association between f variant and urolithiasis. But the mechanism was unknown. The functional studies of VDR *FokI* polymorphism are still required. In addition, more studies are needed to confirm our results.

Our meta-analysis included a total of 23 case-control studies with 3046 cases and 3206 controls, while a previous meta-analysis by Lin et al. [48] only included 17 case-control studies with 2046 cases and 2303 controls. They found significant associations between *FokI* and *TaqI* polymorphisms and urolithiasis risk. However, we found *Apal* and *TaqI* polymorphisms were significantly

associated with urolithiasis risk. More case-control studies were included in our meta-analysis than Lin's study. Therefore, our study may be more powerful and the conclusion might be more reliable. This reason might explain the difference between these two meta-analyses. In addition, our study had some advantages. First, Lin and coworkers tested multiple genetic models, including allelic comparison, a dominant model, and a recessive model. However, they did not correct for multiple comparisons or give biologic rationale for the choice of these genetic models. When the underlying genetic model is unknown, it is better to use pairwise comparisons of the three genotypes to find the best genetic model [34]. We used this method to avoid the problem of multiple comparisons. Second, it was the first time studying the VDR-hypercalciuria interactions on urolithiasis risk. Third, we explored the haplotype effect of *Apal* and *TaqI* polymorphisms on the susceptibility to urolithiasis. Finally, the methodological issues for meta-analysis, such as, quality assessment was well investigated.

We should point out the importance of heterogeneity and publication bias, which might influence the results of meta-analysis. In our study, significant heterogeneity was found in the *BsmI* and *FokI* polymorphisms. Subgroup analysis was used to explore the sources of heterogeneity. After subgroup analysis by the calciuria level, the heterogeneity was effectively disappeared in hypercalciuric patients. Thus, it could be presumed that the relatively large heterogeneity mainly resulted from the calciuria level. In addition, funnel plot and Egger's tests were used to find potential publication bias. No significant publication bias was detected.

Some limitations of our study should be addressed. First, the number of studies that were included in this meta-analysis was moderate. It was possible that some relevant published studies or unpublished studies with negative results were missed. Second, all of the studies were performed in Asians and Caucasians; thus, our results may be applicable only to these ethnic groups. Third, this study did not address gene-gene and gene-environment interactions, because insufficient information could be extracted from the original publications. Fourth, the data of the stone types and biochemical profiles was not showed in our meta-analysis because of insufficient information from the primary publications. Finally, we could not investigate the association between the haplotypes of the *Apal*, *BsmI*, and *TaqI* polymorphisms and urolithiasis risk.

## Conclusions

To our knowledge, this was the most comprehensive meta-analysis to assess the relationship between the VDR polymorphisms and urolithiasis susceptibility. Our results indicated that the *Apal* and *TaqI* polymorphisms

were associated with the risk of urolithiasis. Haplotype analysis suggested that *ApaI-TaqI* haplotypes conferred the susceptibility to urolithiasis. Future large-scale studies with more ethnic groups are needed to validate our findings. Gene-gene and gene-environment interactions should also be considered in future studies.

#### Competing interests

The authors have declared that no competing interests exist.

#### Authors' contributions

PZ and WN collected the literature data, developed the statistical model, carried out the software implementation and drafted the manuscript. All authors read and approved the final manuscript.

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