Yiwei Lin Qiqi Mao
 Xiangyi Zheng Hong Chen
 Kai Yang Liping Xie

Department of Urology, The First
 Affiliated Hospital, School of Medicine,
 Zhejiang University, Hangzhou,
 PR China

Vitamin D Receptor Genetic Polymorphisms and the Risk of Urolithiasis: A Meta-Analysis

Key Words

Vitamin D receptor • Urolithiasis • Etiology • Polymorphism • Meta-analysis

Abstract

Objective: Genetic variants of vitamin D receptor (VDR) were implicated in urolithiasis susceptibility in several case-control studies. However, these studies so far have provided conflicting results. In order to investigate the potential relationship, a meta-analysis was conducted. **Methods:** Eligible studies were retrieved via both computerized searches and review of references. The relation of VDR polymorphisms to urolithiasis was quantified on *Apal*, *BsmI*, *FokI* and *TaqI* separately. Stratified analyses on regional characteristics and stone composition were also performed. Estimates of OR with 95% CI were summarized using the fixed- or random-effect models as appropriate. **Results:** A total of 17 studies were included in our analysis. There was no evidence showing significant associations between *Apal* and *BsmI* polymorphisms and urolithiasis risk in overall estimates. However, f allele and ff+Ff genotype in the dominant model of *FokI* were related with an increase of urolithiasis risk. *TaqI* also presented with increased urolithiasis risk with t allele and tt+Tt genotype in the dominant model. **Conclusion:** Our meta-analysis indicated VDR polymorphisms could be potential biomarkers for urolithiasis susceptibility.

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Introduction

Urolithiasis is associated with many complicated factors. It can be triggered by environmental influences, metabolic defects and genetic factors [1, 2]. The tendency of stone formation is largely attributed to excessive calcium absorption, since calcium is the principal crystalline constituent in up to 80% of kidney stones [2]. VDR is a 50- to 60-kDa cellular polypeptide that plays a central role in mineral metabolism, including calcium homeostasis and tubular citrate handling. It could facilitate the active form of vitamin D with calcium absorption and citrate excretion [3, 4]. Any alteration in the vitamin D receptor (VDR) may change the mineral metabolism, thus consequently be associated with altered urolithiasis risk.

A growing amount of epidemiologic evidence has suggested that allelic variations in the VDR gene may be involved in the etiology of urinary stone disease. The four most common single nucleotide polymorphisms (SNPs), i.e., *Apal*, *BsmI*, *TaqI* and *FokI*, which were hypothesized to influence the expression and/or function of the VDR protein [4–6], had earned the focus in a search for candidate genetic markers associated with urolithiasis. *Apal*, *BsmI* and *TaqI* located in the 3' UTR region of the VDR gene were supposed to affect the mRNA stability or change vitamin D activity via translation regulation [4]. *FokI* located in the exon 2. It was functionally significant

and associated with transactivation of the vitamin D signal [5]. Numerous studies have been dedicated to interpreting the possible association between the mentioned polymorphisms and urolithiasis susceptibility. However, the results were inconclusive. For instance, Jackman et al. [7] observed that the TT genotype in *TaqI* polymorphism was associated with more aggressive stone disease, both within families and with respect to recurrence. Mossetti et al. [8] found associations between the *BsmI* and *TaqI* polymorphisms and idiopathic hypocitraturia in recurrent calcium oxalate stone disease. The most recent study by Mittal et al. [9] indicated that both Tt genotype of *TaqI* polymorphism and Ff of *FokI* polymorphism demonstrated a significantly higher risk for stone formation (OR = 1.830 and 3.559, respectively). However, the analysis by Chen et al. [10] revealed that the *BsmI* polymorphism of the VDR gene was not a suitable genetic marker for urinary stone disease. Seo et al. [11] and Gunes et al. [12] reported that VDR polymorphisms did not confer a significant risk for urinary stones.

The controversial results across many of these studies could possibly be related to the small sample size from an individual study, ethnic difference or the biological genetic model applied for the analysis. Therefore, it was necessary to quantify the potential between-study heterogeneity and summarize results from all eligible studies with rigorous methods. In the present study, a meta-analysis with the most updated data was performed to revisit the association between VDR variants (i.e., *ApaI*, *BsmI*, *FokI* and *TaqI*) and urolithiasis risk.

Materials and Methods

Literature Search

The studies considered in this meta-analysis were case-control studies exploring the association between VDR polymorphic sites *ApaI*, *BsmI*, *TaqI* and *FokI*, and urolithiasis risk. An initial literature search was conducted within the PubMed database up to September 2010, using MeSH terms, 'urolithiasis', 'vitamin D', and 'receptors, calcitriol'. Additional studies were identified from references cited in retrieved articles. Eligible studies had to fulfill all the following inclusion criteria: (a) case-control study evaluating the association between VDR polymorphisms and urolithiasis risk, (b) the polymorphic sites should include at least one of the mentioned sites, i.e. *BsmI*, *ApaI*, *FokI* or *TaqI*, and (c) distribution of each genotype in patients and controls should be determined. In studies with overlapping patients or controls, only the latest or the most complete was included. Any study with inconsistent or erroneous data was excluded. Meeting abstracts with insufficient data or unpublished reports were not considered.

Data Extraction

Two investigators independently extracted data from all potentially relevant studies. Conflicting evaluations were resolved by discussion. When needed, the third-party resolution was sought. Data extracted from these articles included the name of the first author, year of publication, number of cases and controls, region/ethnicity, and genotype frequencies for cases and controls.

Statistical Analysis

OR and 95% CI were estimated for the strength of the association between *ApaI*, *BsmI*, *TaqI* and *FokI* polymorphisms and urolithiasis risk respectively. The pooled ORs were performed for allelic comparison, a dominant model, and a recessive model in each of the above polymorphic sites [13, 14]. Between-study heterogeneity across the eligible comparisons was quantitatively assessed using the χ^2 -based Q statistical test and I^2 test [15, 16]. Heterogeneity was considered significant when $p < 0.05$. The data from single comparison was combined using fixed-effect model with the Mantel-Haenszel method [17] when no heterogeneity presented. Otherwise, the random-effect model with the DerSimonian-Laird method [18] was used for pooling. The potential publication bias was estimated statistically by Egger's test [19]. Considering the capacity of bias detection, the publication bias was only computed for the analysis including more than 8 studies [19]. $p < 0.05$ was considered indicative of significant publication bias. To test for population stratification, the distributions of genotypes in the controls were tested for Hardy-Weinberg equilibrium (HWE). Regarding the impact of HWE, studies with the controls not in HWE were subjected to a sensitivity analysis [14]. In addition, subgroups in terms of ethnics or stone composition were stratified. Those with more than 2 studies were summarized. All statistical analyses were performed with STATA version 10.1 (StataCorp, College Station, Tex., USA). All p values were two-sided.

Results

Eligible Studies

A total of 22 eligible articles were retrieved [7–12, 20–35]. Three studies [8, 27, 32] with overlapping data were discussed in detail for inclusion. Those with a control group in HWE were considered higher priority [27, 32]. The study with mistyped data [30] and the studies without a control group [22, 24, 35] were excluded. Finally, 17 studies (table 1) were included in our meta-analysis. There were 7 exploring the association between *ApaI* polymorphism and urolithiasis, 6 for *BsmI*, 9 for *FokI*, and 9 for *TaqI*. Since most studies did not provide details on ethnic features, ethnic subgroup analysis should be done according to the regional characteristics, which would instead be stratified as Asia, America and Europe. Subgroup analysis on calcium stone should also be performed with studies providing specified stone composition data according to either calculous analysis or imaging.

Table 1. List and characteristics of studies included in the meta-analysis

Year	Reference (first author)	Region	Stone composition ¹	Cases	Controls	Polymorphic sites (HWE status ²)
1999	Ruggiero [20]	Europe	NS	27	150	<i>BsmI</i> (N)
1999	Jackman [7]	America	Calcium	17	37	<i>TaqI</i> (N)
2001	Chen [10]	Asia	Calcium	124	90	<i>BsmI</i> (N)
2001	Chen [21]	Asia	Calcium	146	90	<i>FokI</i> (Y)
2002	Nishijima [23]	Asia	Calcium	83	83	<i>ApaI</i> (Y), <i>TaqI</i> (Y)
2003	Ozkaya [25]	Europe	Calcium	64	90	<i>ApaI</i> (N), <i>BsmI</i> (Y), <i>TaqI</i> (Y)
2003	Wang [34]	Asia	Calcium	150	80	<i>ApaI</i> (Y), <i>FokI</i> (Y), <i>TaqI</i> (Y)
2004	Mossetti [32]	Europe	Calcium	110	127	<i>TaqI</i> (Y)
2004	Rendina [27]	Europe	Calcium	159	124	<i>ApaI</i> (Y), <i>BsmI</i> (Y), <i>FokI</i> (Y)
2004	Relan [26]	Asia	Calcium	150	100	<i>BsmI</i> (N), <i>FokI</i> (N)
2005	Bid [28]	Asia	Calcium	50	60	<i>FokI</i> (N)
2005	Bid [33]	Asia	Calcium	138	166	<i>FokI</i> (N)
2006	Gunes [12]	Europe	Calcium	110	150	<i>ApaI</i> (Y), <i>BsmI</i> (Y), <i>TaqI</i> (Y)
2007	Liu [29]	Asia	Calcium	235	231	<i>FokI</i> (Y)
2007	Seyhan [31]	Europe	Calcium	80	40	<i>TaqI</i> (N)
2009	Seo [11]	Asia	NS	278	535	<i>ApaI</i> (N), <i>FokI</i> (N), <i>TaqI</i> (N)
2010	Mittal [9]	Asia	NS	125	150	<i>ApaI</i> (Y), <i>FokI</i> (N), <i>TaqI</i> (Y)

¹ 'NS' indicates stone composition was not specified, while 'Calcium' indicates calcium stone.

² 'N' indicates the genotype distribution of the corresponding control group deviated from HWE, 'Y' indicates the consistence with HWE.

ApaI Polymorphism

Seven studies associating *ApaI* and urolithiasis risk were identified from the literature search. Between-study heterogeneity was detected only in the dominant genetic model for the Europe subgroup ($P_{\text{heterogeneity}} = 0.014$, $I^2(\%) = 76.7$) and calcium stone subgroup ($P_{\text{heterogeneity}} = 0.027$, $I^2(\%) = 63.5$), so the DerSimonian-Laird method for the random-effect model was applied in these subgroup analyses. The pooled OR from overall studies indicated no significant association between *ApaI* polymorphisms and urolithiasis risk in allelic comparison (OR = 0.94, 95% CI 0.83, 1.07), dominant model (OR = 0.91, 95% CI 0.75, 1.10) or recessive model (OR = 0.96, 95% CI 0.76, 1.21). Sensitivity analysis after excluding the studies with controls deviating from HWE did not alter the pattern of results (table 2). Also, no specific relationship between *ApaI* polymorphism and calcium stone was found in any of the above comparisons (table 2). Furthermore, a regional specific subgroup analysis could not detect any significant association (table 2).

BsmI Polymorphism

A similar result to *ApaI* polymorphism was obtained after summarizing 6 studies exploring the association be-

tween *BsmI* polymorphism and urolithiasis risk. No significant association in pooled OR for overall studies was detected in allelic comparison (OR = 1.12, 95% CI 0.94, 1.32), dominant model (OR = 1.23, 95% CI 0.92, 1.63) or recessive model (OR = 1.09, 95% CI 0.83, 1.42). The sensitivity analysis results suggested that there was no significant influence of the individual data deviating from HWE set to the overall pooled OR. In the subgroup analyses by region and calcium stone, no significant result was observed either (table 3).

FokI Polymorphism

For the association between *FokI* polymorphism and urolithiasis risk, 9 studies were retrieved. Between-study heterogeneity was considered according to χ^2 -based Q statistical test and I^2 test (table 4). The random-effect model was therefore applied. The summarization of overall studies with allelic comparison (OR = 1.26, 95% CI 1.00, 1.59, $P_{\text{heterogeneity}} < 0.001$, $I^2(\%) = 77.6$) indicated a marginal increased in urolithiasis risk with f allele. However, the overall results from the dominant model (OR = 1.55, 95% CI 0.99, 2.41, $P_{\text{heterogeneity}} < 0.001$, $I^2(\%) = 85.4$) and recessive model (OR = 1.10, 95% CI 0.79, 1.52, $P_{\text{heterogeneity}} = 0.039$, $I^2(\%) = 50.7$) showed no significant

Table 2. Results of allelic and genotypic association analysis for the *ApaI* polymorphism

Category	OR (95% CI)	P _{heterogeneity}	I ² , %
<i>Allelic comparison (a vs. A)</i>			
All	0.94 (0.83, 1.07)	0.294	17.8
Asia	0.94 (0.80, 1.10)	0.431	0
Europe	0.95 (0.77, 1.18)	0.104	55.9
Calcium stone	0.88 (0.74, 1.05)	0.202	32.9
All in HWE	0.95 (0.80, 1.11)	0.524	0
<i>Dominant model (Aa + aa vs. AA)</i>			
All	0.91 (0.75, 1.10)	0.058	50.8
Asia	0.89 (0.71, 1.12)	0.322	14
Europe	0.75 (0.34, 1.66)	0.014	76.7
Calcium stone	0.71 (0.42, 1.19)	0.027	63.5
All in HWE	0.99 (0.76, 1.27)	0.338	11.8
<i>Recessive model (aa vs. AA + Aa)</i>			
All	0.96 (0.76, 1.21)	0.344	11.1
Asia	0.98 (0.74, 1.29)	0.145	44.4
Europe	0.93 (0.63, 1.38)	0.52	0
Calcium stone	0.88 (0.66, 1.16)	0.789	0
All in HWE	0.86 (0.64, 1.14)	0.689	0

Table 3. Results of allelic and genotypic association analysis for the *BsmI* polymorphism

Category	OR (95% CI)	P _{heterogeneity}	I ² , %
<i>Allelic comparison (b vs. B)</i>			
All	1.12 (0.94, 1.32)	0.283	19.9
Asia	1.23 (0.89, 1.70)	0.272	17.1
Europe	1.07 (0.88, 1.31)	0.208	34
Calcium stone	1.08 (0.90, 1.29)	0.301	17.8
All in HWE	1.02 (0.82, 1.27)	0.249	28
<i>Dominant model (Bb + bb vs. BB)</i>			
All	1.23 (0.92, 1.63)	0.398	2.8
Asia	1.44 (0.93, 2.24)	0.116	59.6
Europe	1.09 (0.76, 1.58)	0.636	0
Calcium stone	1.26 (0.94, 1.68)	0.335	12.3
All in HWE	1.13 (0.77, 1.67)	0.502	0
<i>Recessive model (bb vs. BB + Bb)</i>			
All	1.09 (0.83, 1.42)	0.054	54
Asia	1.03 (0.60, 1.76)	0.934	0
Europe	1.28 (0.70, 2.35)	0.013	72.1
Calcium stone	0.98 (0.74, 1.29)	0.516	0
All in HWE	0.96 (0.69, 1.33)	0.201	37.6

Table 4. Results of allelic and genotypic association analysis for the *FokI* polymorphism

Category	OR (95% CI)	P _{heterogeneity}	I ² , %
<i>Allelic comparison (f vs. F)</i>			
All	1.26 (1.00, 1.59)	<0.001	77.6
Asia	1.30 (1.00, 1.68)	<0.001	79.8
Europe	–	–	–
Calcium stone	1.24 (0.92, 1.69)	<0.001	80.3
All in HWE	1.07 (0.76, 1.50)	0.002	76.5
<i>Dominant model (Ff + ff vs. FF)</i>			
All	1.55 (0.99, 2.41)	<0.001	85.4
Asia	1.65 (1.00, 2.72)	<0.001	86.7
Europe	–	–	–
Calcium stone	1.50 (0.88, 2.55)	<0.001	84.5
All in HWE	1.08 (0.67, 1.75)	0.006	72.1
<i>Recessive model (ff vs. FF + Ff)</i>			
All	1.10 (0.79, 1.52)	0.039	50.7
Asia	1.09 (0.75, 1.58)	0.024	50.7
Europe	–	–	–
Calcium stone	1.08 (0.70, 1.64)	0.025	58.5
All in HWE	1.04 (0.61, 1.76)	0.018	66.4

Table 5. Results of allelic and genotypic association analysis for the *TaqI* polymorphism

Category	OR (95% CI)	P _{heterogeneity}	I ² , %
<i>Allelic comparison (t vs. T)</i>			
All	1.15 (1.00, 1.34)	0.869	0
Asia	1.23 (0.99, 1.52)	0.567	0
Europe	1.09 (0.88, 1.35)	0.754	0
America	–	–	–
Calcium stone	1.16 (0.98, 1.38)	0.718	0
All in HWE	1.15 (0.98, 1.36)	0.674	0
<i>Dominant model (Tt + tt vs. TT)</i>			
All	1.28 (1.05, 1.56)	0.811	0
Asia	1.40 (1.07, 1.82)	0.621	0
Europe	1.11 (0.81, 1.52)	0.7	0
America	–	–	–
Calcium stone	1.26 (0.98, 1.61)	0.758	0
All in HWE	1.34 (1.07, 1.69)	0.656	0
<i>Recessive model (tt vs. TT + Tt)</i>			
All	1.04 (0.77, 1.40)	0.254	21.3
Asia	0.95 (0.58, 1.56)	0.35	8.5
Europe	1.15 (0.78, 1.71)	0.101	51.9
America	–	–	–
Calcium stone	1.15 (0.83, 1.60)	0.192	31
All in HWE	0.96 (0.69, 1.33)	0.464	0

association between *FokI* polymorphism and urolithiasis risk. Sensitivity analysis by excluding the studies with controls deviating from HWE suggested no evidence of alteration in the association, with an insignificant association for the summarization of studies in HWE (table 4). In the further regional specific stratified analysis, the Ff+ff genotype in the dominant genetic model (OR = 1.65, 95% CI 1.00, 2.72, $P_{\text{heterogeneity}} < 0.001$, $I^2(\%) = 86.7$) and f allelic (OR = 1.30, 95% CI 1.00, 1.68, $P_{\text{heterogeneity}} < 0.001$, $I^2(\%) = 79.8$) presented with a marginally positive relationship to susceptibility for urolithiasis in the Asia subgroup (table 4). Publication bias of the overall analysis in three comparison models was assessed by Egger's test separately. No publication bias was detected according to Egger's test (allelic comparison: $p = 0.297$; dominant model: $p = 0.183$; recessive model: $p = 0.296$).

TaqI Polymorphism

When all of the 9 studies were pooled, no significant between-study heterogeneity was detected (table 5). Marginal positive association was found between the *TaqI* polymorphism and urolithiasis risk in overall allelic comparison (OR = 1.15, 95% CI 1.00, 1.34), while the pooled analyses in the dominant model and recessive model were insignificant (OR = 1.28, 95% CI 1.05, 1.56; OR = 1.04, 95% CI 0.77, 1.40, respectively). However, sensitivity analysis after excluding all the studies with controls deviating from HWE indicated an increased urolithiasis risk associated with tt+Tt genotype in the dominant model (OR = 1.34, 95% CI 1.07, 1.69). Stratified analysis according to the regional characteristics suggested a similar significant association in the dominant genetic model in the Asia subgroup (OR = 1.40, 95% CI 1.07, 1.82) while the other subgroups yielded insignificant results (table 5). Further calcium stone-specific association also yielded insignificant results (table 5). In Egger's test for publication bias of the overall analysis, no bias was detected (allelic comparison: $p = 0.481$; dominant model: $p = 0.667$; recessive model: $p = 0.578$).

Discussion

It is quite reasonable to identify a genetic marker with a significant relationship to susceptibility for urinary stone disease. A well-established genetic marker surely would have a profound influence in screening and prevention of urolithiasis [36, 37], even though the diagnosis of urolithiasis mostly depends on imaging. A lot of genetic epidemiological studies have been conducted to ex-

plore the relationship between SNPs and urolithiasis. A wide range of genetic markers have been examined, including polymorphisms of genes coding for the VDR [7–12, 20–35], interleukin [38, 39], fibronectin [40] and urokinase [41–43]. As one of the most important genes related with calcium metabolism, VDR gene has earned special concern. Biological evidence has clearly illustrated the role of VDR in calcium metabolism [44]. In the genetic hypercalciuric rat model, Li et al. [45] found that increase in the number of intestinal VDR was associated with increased calcium absorption. The epidemiological data from Zhu et al. [46] indicated a genetic association between *BsmI*, *FokI* and *TaqI* VDR polymorphisms and idiopathic hypocitraturia. The study by Ferreira et al. [35] suggested that bb homozygous for *BsmI* polymorphisms in VDR was overrepresented in hypercalciuric stone formers. However, genetic epidemiological studies investigating urolithiasis markers yielded conflicting results, which indicated that identifying a genetic marker for urolithiasis remains a big challenge.

Herein, we quantitatively summarized all these epidemiological studies to provide an evidence-based clue for the genetic markers located on VDR gene for urolithiasis. To the best of our knowledge, our current meta-analysis was the first quantitative summarization examining four well-characterized SNPs of the VDR gene for their relevance to urolithiasis. This meta-analysis examined the *ApaI*, *BsmI*, *FokI* and *TaqI* polymorphisms of the VDR gene and their relationship to urolithiasis. The associations for the allele contrast, the dominant model and recessive model were examined.

In our analysis, both *ApaI* and *BsmI* were not associated with urolithiasis risk. The sensitivity analysis for the studies not in HWE did not alter the insignificant results. Further quantitative assay stratified by regional information and stone type also yielded null results. These results could be reinforced by previous studies [47] which proposed that absorptive hypercalciuria (a stone-forming condition) was not attributable to variation of the VDR genotypes. However, it should still be interpreted with caution considering the limited number of primary studies. The null results could possibly be due to an inadequate number of primary studies to detect the strength of the postulated associations. Also, there existed a possibility that the complex etiology of urolithiasis which included diet and living habits would probably mask the positive association while a single study in our analysis could not provide sufficient information. While *FokI* was analyzed, our result demonstrated a marginal effect of *FokI* polymorphism on the risk of urolithiasis. However, se-

vere between-study heterogeneity was found. One of the most critical factors contributing to such heterogeneity might be the diverse genotype distributions of *FokI* in studies. Also, the uneven selection criteria for the case and control in different studies would generate heterogeneity. Even though derived from a set of heterogeneous studies, the results from the Asia subgroup revealed an increased urolithiasis risk with ff+Ff genotype in the dominant model or f allele in allelic comparison. The positive association was also found in overall allelic comparison. Several arguments contradicted these findings. Jurutka et al. [48] found that F allele interacted more efficiently with basal transcription factor IIB and possessed higher transcriptional activity. Similarly, in the molecular research done by Whitfield et al. [6], the 424-amino-acid short VDR variant (corresponding to the 'F' allele) represented a more transcriptionally potent VDR protein. An epidemiological study by Liu et al. [29] also suggested F allele would carry a greater hazard regarding stone episodes and the age of the first stone onset. The confusing results surely indicated a further functional study on *FokI* polymorphism. In the quantitative assay for *TaqI* polymorphism, a mild increase in urolithiasis risk was found in the tt+Tt genotype compared with TT. The result remained stable in the sensitivity analysis and the Asia subgroup. A marginal increase in urolithiasis risk with t allele in allelic comparison was also detected. However, the Europe subgroup analysis did not support

the effect of t allele in urolithiasis risk, which indicated a possible difference in genetic background.

Despite the findings from our current analysis, we still have to acknowledge several limitations. Meta-analysis cannot correct all the biases of individual studies. Considering the multifactorial etiology in urolithiasis, a more precise assay should be based on adjusted estimates according to covariates such as age, lifestyle and environmental factors. We have made many efforts including testing the publication bias, conducting sensitivity and subgroup analysis to acquire a more accurate estimate. However, regional information cannot completely represent an ethnic group's genetic background and strong linkage disequilibrium exists among *ApaI*, *BsmI* and *TaqI* [4, 49]. Furthermore, this linkage disequilibrium varied in different ethnic groups [49]. These would probably bias our results. Many more well-designed case-control studies with more detailed information are needed to investigate the potential multigenetic predisposition of the disease and to validate our findings.

In summary, evidence from our meta-analysis supports the fact that some VDR gene polymorphisms are associated with an increase in the probability of urolithiasis with certain populations under an indicated genetic model. Considering the predictive value, it warrants further investigation to better clarify these SNP-urolithiasis associations and to reinforce our findings.

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