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Relationship between vitamin D (1,25-dihydroxyvitamin D3) receptor gene polymorphisms and primary biliary cirrhosis risk: a meta-analysis

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ABSTRACT. The vitamin D (1,25-dihydroxyvitamin D3) receptor (*VDR*) gene encodes a protein that functions in the transcriptional regulation of vitamin D-responsive genes and plays a role in innate immunity and adaptive immune responses. In this study, we investigated the relationship between *VDR* polymorphisms (*Bsm*I, *Apa*I, and *Taq*I) and primary biliary cirrhosis (PBC) risk. We conducted an overall meta-analysis and subgroup meta-analysis based on ethnicity that included a total of 6 eligible studies (672 cases and 1148 controls). We detected no significant PBC risk variation for all genetic models in the overall analysis and in the subgroup analysis based on ethnicity for the *Bsm*I polymorphism. For the *Apa*I polymorphism, significant associations were observed in the overall analysis as well as in the Asian subgroup. Furthermore, in the subgroup analysis based on ethnicity, a significant association was observed in the Caucasian subgroup but not in the Asian subgroup for the *Taq*I polymorphism. Based on the results of our meta-analysis, the *VDR Bsm*I polymorphism may not be associated

with PBC risk, while the *VDR Apa*I polymorphism is likely associated with PBC risk, particularly in Asians. The *VDR Taq*I polymorphism may be associated with PBC risk in Caucasians.

Key words: Meta-analysis; Polymorphism; Primary biliary cirrhosis risk; *VDR*

INTRODUCTION

The vitamin D (1,25-dihydroxyvitamin D3) receptor (*VDR*) gene encodes a protein that belongs to the nuclear hormone receptor superfamily and functions in the transcriptional regulation of vitamin D-responsive genes (Cantorna, 2006; Adorini and Penna, 2008). VDR-mediated signaling plays a role in innate immunity and adaptive immune responses (Adorini and Penna, 2008). Three polymorphisms (*Bsm*I, rs1544410, in intron 8; *Apa*I, rs7975232, in intron 8; and *Taq*I, rs731236, in exon 9) of the *VDR* gene have been widely studied in autoimmune diseases (Uitterlinden et al., 2004b; Guo et al., 2006; Valdivielso and Fernandez, 2006; Zhou et al., 2009; Lee et al., 2011; Huang and Xie, 2012; Feng et al., 2013).

In this study, we investigated the association between the 3 *VDR* polymorphisms (*Bsm*I, *Apa*I, and *Taq*I) and primary biliary cirrhosis (PBC) risk. PBC is a chronic cholestatic liver disease with strong autoimmune features (Poupon, 2010; Hirschfield and Invernizzi, 2011). Over the past decade, several studies have focused on the relationship between *VDR* polymorphisms (*Bsm*I, *Apa*I, and *Taq*I) and PBC risk, but the results of individual studies have provided limited information (Halmos et al., 2000; Lakatos et al., 2002; Vogel et al., 2002; Fan et al., 2005; Tanaka et al., 2009; Kempińska-Podhorecka et al., 2012). Therefore, we performed a meta-analysis with a relatively large sample size of 6 eligible studies (672 cases and 1148 controls) to determine the relationship between *VDR* polymorphisms (*Bsm*I, *Apa*I, *and Taq*I) and PBC risk.

MATERIAL AND METHODS

The workflow of this study is shown in Figure 1.

Literature search, selection, and data collection

In this study, we searched for papers published before August 30, 2013 using the key words “VDR” or “vitamin D (1,25-dihydroxyvitamin D3) receptor”, “primary biliary cirrhosis” or “PBC”, and “polymorphism” in 3 widely used databases (PubMed, Web of Science, and EBSCO). Identified studies were further selected for meta-analysis using the following selection criteria: i) full-text studies written in English, ii) study providing complete case and control data regarding the relationship between *VDR* polymorphisms and PBC risk, iii) studies sharing the same sample of cases and controls were compared, with the most complete study included in our meta-analysis.

In this study, 2 investigators independently collected data from each eligible paper. Data collected included first author, published year, country of origin, ethnicity, source of controls, and numbers of cases and controls. Final selection of studies was based on agreement between the 2 investigators.

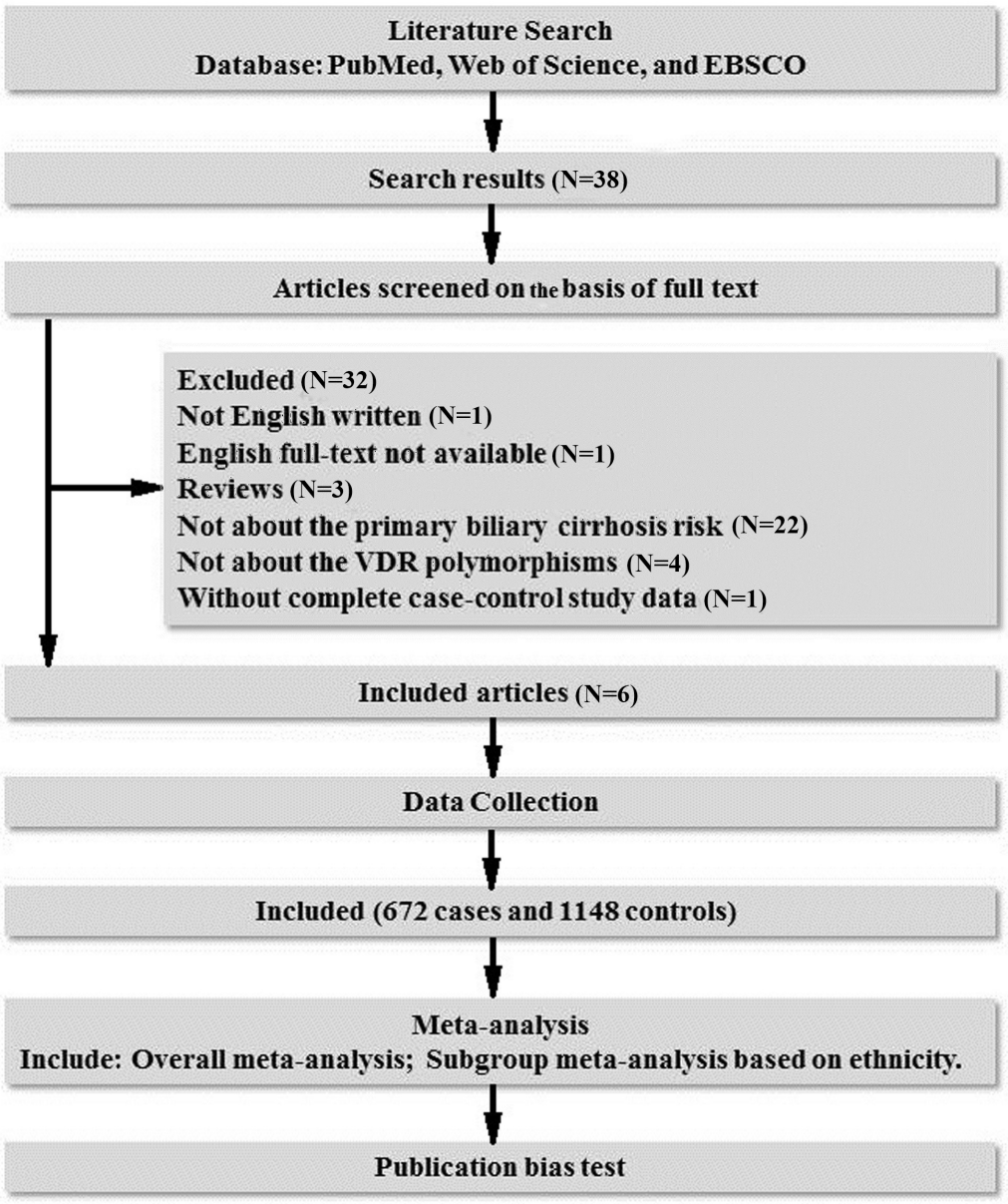

Figure 1. Workflow chart of this study.

Meta-analysis methods

Using the data collected from each paper, we performed both the overall meta-analysis and the subgroup meta-analysis based on ethnicity to evaluate the relationship between *VDR* polymorphisms and PBC risk. In the overall as well as the subgroup meta-analysis,

pooled odds ratios (ORs) and 95% confidence intervals (CIs) for dominant, recessive, and codominant genetic models were calculated using the fixed-effect model or the random-effect model. The model chosen was based on the heterogeneity test. For the heterogeneity test, we performed the χ^2-based *Q*-test (Lau et al., 1997). When the *Q*-test reported a P value of more than 0.10, the fixed-effect model was used to calculate the pooled ORs (Mantel and Haenszel, 1959); otherwise, the random-effect model was used (DerSimonian and Laird, 1986).

Publication bias was also tested using Begg's funnel plot and the Egger test (Egger et al., 1997). If the funnel plot was asymmetric and the Egger test reported a P value of less than 0.05, publication bias was likely to exist.

Stata version 10.0 (Stata Corporation, College Station, TX, USA) was used for the meta-analysis.

RESULTS

Studies and data included in this meta-analysis

Search and selection identified 6 eligible studies for the meta-analysis (Halmos et al., 2000; Lakatos et al., 2002; Vogel et al., 2002; Fan et al., 2005; Tanaka et al., 2009; Kempińska-Podhorecka et al., 2012). All 6 studies collected were case-control studies and included various ethnicities (1 study of Asians, 4 studies of Caucasians, and 1 study of both Asians and Caucasians) and source of controls (5 studies of population-based controls, and 1 study of both hospital-based and population-based controls). Information from these 6 studies and the numbers of cases and controls with different genotypes reported in each study are presented in Table 1. The 6 eligible studies included 672 cases and 1148 controls to examine the relationship between *VDR* polymorphisms and PBC risk.

Table 1. Studies and data included in this meta-analysis.

First author	Published year	Country of origin	Ethnicity controls	Source	Cases	Controls
*Bsm*I (rs1544410)					*AA/AG/GG*	*AA/AG/GG*
Halmos	2000	Hungary	Caucasian	Population	14/9/7	8/24/19
Lakatos	2002	Hungary	Caucasian	Population	19/11/3	23/41/18
Vogel	2002	Germany	Caucasian	Hospital and Population	16/23/35	42/108/64
Fan	2005	China	Asian	Population	0/3/55	3/28/129
Tanaka[a]	2009	Japan	Asian	Population	14/37/144	1/35/143
Tanaka[a]	2009	Italy	Caucasian	Population	56/78/5	42/98/16
Kempińska-Podhorecka	2012	Poland	Caucasian	Population	20/75/48	95/135/76
*Apa*I (rs7975232)					*TT/TG/GG*	*TT/TG/GG*
Vogel	2002	Germany	Caucasian	Hospital and Population	18/33/23	56/116/42
Fan	2005	China	Asian	Population	7/25/26	18/66/76
Tanaka[a]	2009	Japan	Asian	Population	104/27/64	63/43/73
Tanaka[a]	2009	Italy	Caucasian	Population	65/55/19	71/64/21
Kempińska-Podhorecka	2012	Poland	Caucasian	Population	40/80/23	75/161/65
*Taq*I (rs731236)					*TT/TC/CC*	*TT/TC/CC*
Vogel	2002	Germany	Caucasian	Hospital and Population	39/23/12	87/99/31
Fan	2005	China	Asian	Population	53/5/0	143/13/4
Tanaka[a]	2009	Japan	Asian	Population	152/43/0	150/26/3
Tanaka[a]	2009	Italy	Caucasian	Population	54/63/22	61/69/26
Kempińska-Podhorecka	2012	Poland	Caucasian	Population	20/77/46	100/140/37

[a]The article Tanaka et al. (2009) investigated 2 populations and was treated as 2 independent studies in both overall analysis and subgroup analysis based on ethnicity.

Overall and subgroup meta-analysis results

In this study, we performed both overall meta-analysis and subgroup meta-analysis based on ethnicity. The detailed results of our meta-analysis are shown in Table 2 and Figure 2. First, the overall meta-analysis and subgroup meta-analysis based on ethnicity revealed no association between the *VDR Bsm*I polymorphism and PBC risk for all genetic models (Table 2). Second, the results of the overall meta-analysis provided some evidence of an association between the *VDR Apa*I polymorphism and PBC risk (OR = 1.31, 95%CI = 1.04-1.64 for TT *vs* TG + GG; Table 2 and Figure 2). In the subgroup meta-analysis based on ethnicity for the *Apa*I polymorphism, significantly increased PBC risks were also detected in Asians for TT *vs* GG (OR = 1.72, 95%CI = 1.14-2.60; Table 2) and for TT *vs* TG + GG (OR = 1.88, 95%CI = 1.29-2.74; Table 2 and Figure 2), while in Caucasians no such association was observed. Third, the results of the overall meta-analysis revealed no association between the *VDR Taq*I polymorphism and PBC risk for all genetic models (Table 2). However, in the subgroup meta-analysis based on ethnicity, a significant association between the *VDR Taq*I polymorphism and PBC risk was observed in Caucasians (OR = 0.62, 95%CI = 0.43-0.89 for TC *vs* CC; Table 2). Based on the results of our meta-analysis, the *VDR Bsm*I polymorphism may not be associated with PBC risk, while the *VDR Apa*I polymorphism is likely associated with PBC risk, particularly in Asians, and the T allele acts as a risk factor. Additionally, the C allele of the *VDR Taq*I polymorphism may also act as a PBC risk factor in Caucasians.

Table 2. Detailed results of meta-analysis.

Meta-analysis models	Overall analysis		Subgroup analysis based on ethnicity			
			Asian		Caucasian	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
*Bsm*I (rs1544410)						
AA *vs* GG	1.92 (0.65-5.71)[a]	0.000	2.54 (0.07-97.29)[a]	0.043	1.71 (0.54-5.48)[a]	0.000
AG *vs* GG	0.84 (0.52-1.37)[a]	0.015	0.57 (0.14-2.33)[a]	0.034	0.95 (0.51-1.77)[a]	0.023
AA + AG *vs* GG	1.02 (0.57-1.82)[a]	0.000	0.62 (0.10-3.76)[a]	0.006	1.20 (0.59-2.45)[a]	0.002
AA *vs* AG + GG	1.76 (0.76-4.09)[a]	0.000	2.73 (0.08-90.33)[a]	0.051	1.56 (0.65-3.78)[a]	0.000
*Apa*I (rs7975232)						
TT *vs* GG	1.21 (0.80-1.83)[a]	0.100	1.72 (1.14-2.60)[b]	0.361	1.02 (0.69-1.51)	0.154
TG *vs* GG	0.91 (0.69-1.20)	0.171	0.87 (0.57-1.34)	0.326	0.90 (0.49-1.63)[a]	0.068
TT + TG *vs* GG	1.07 (0.76-1.51)[a]	0.097	1.30 (0.92-1.84)	0.530	0.92 (0.51-1.66)[a]	0.054
TT *vs* TG + GG	1.31 (1.04-1.64)[b]	0.105	1.88 (1.29-2.74)[b]	0.201	1.06 (0.80-1.41)	0.804
*Taq*I (rs731236)						
TT *vs* CC	0.89 (0.27-2.91)[a]	0.000	4.88 (0.60-39.53)	0.726	0.57 (0.16-2.10)[a]	0.000
TC *vs* CC	0.80 (0.41-1.56)[a]	0.055	6.71 (0.79-56.88)	0.603	0.62 (0.43-0.89)[b]	0.114
TT + TC *vs* CC	0.84 (0.38-1.87)[a]	0.006	5.11 (0.63-41.35)	0.695	0.65 (0.30-1.43)[a]	0.006
TT *vs* TC + CC	0.82 (0.44-1.52)[a]	0.000	0.78 (0.49-1.23)	0.305	0.78 (0.29-2.09)[a]	0.000

OR = odds ratio; CI = confidence interval; P: P values for heterogeneity test. If P > 0.1, ORs were calculated using the fixed-effect model, otherwise the random-effect model was used. [a]ORs calculated using the random-effect model. [b]Results which are statistically significant.

Publication bias test results

For the 3 *VDR* polymorphisms (*Bsm*I, *Apa*I, and *Taq*I), the results of Begg's funnel plot (data not shown) and Egger test (Table 3) showed no publication bias under dominant, recessive, and codominant models in the overall meta-analysis.

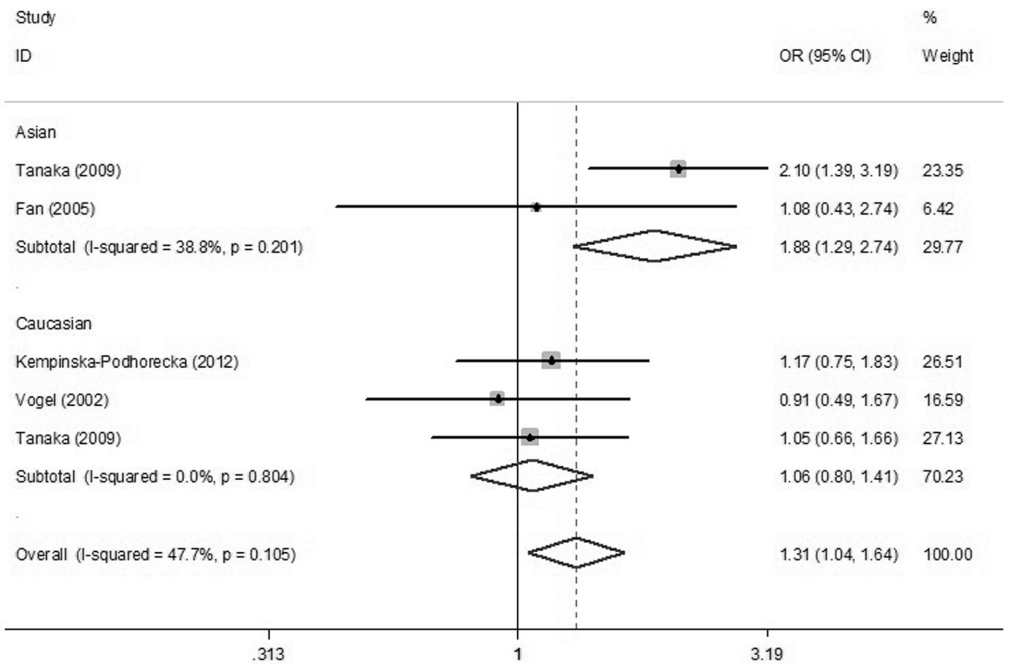

Figure 2. Forest plot of the overall meta-analysis and subgroup meta-analysis based on ethnicity for *VDR Apa*I polymorphism (TT *vs*TG + GG). All ORs and 95%CIs shown in this plot were calculated using the fixed-effect model.

Table 3. Publication bias analysis results.

Meta-analysis models	P
*Bsm*I (rs1544410)	
AA *vs* GG	0.10
AG *vs* GG	0.85
AA + AG *vs* GG	0.47
AA *vs* AG + GG	0.39
*Apa*I (rs7975232)	
TT *vs* GG	0.18
TG *vs* GG	0.56
TT + TG *vs* GG	0.27
TT *vs* TG + GG	0.43
*Taq*I (rs731236)	
TT *vs* CC	0.41
TC *vs* CC	0.12
TT + TC *vs* CC	0.20
TT *vs* TC + CC	0.84

P = P values for the Egger test. If $P < 0.05$, the publication bias likely exists.

DISCUSSION

In this study, the results of our overall meta-analysis and subgroup meta-analysis based on ethnicity revealed no association between the *VDR Bsm*I polymorphism and PBC risk. However, the results of overall meta-analysis and subgroup meta-analysis based on ethnicity suggested that the *VDR Apa*I polymorphism is significantly associated with PBC risk,

particularly in Asians. Moreover, our subgroup meta-analysis based on ethnicity revealed that the *VDR Taq*I polymorphism C allele may act as a PBC risk factor in Caucasians. These results suggest that the *VDR Apa*I and *Taq*I polymorphisms may not function independently in PBC development; instead, combined effects of those polymorphisms with other biological and environmental factors, which are different between ethnicities, probably exist. The *VDR Apa*I polymorphism is reportedly located in intron 8, while the *Taq*I polymorphism leads to a silent mutation in exon 9 (Uitterlinden et al., 2004a; Kempińska-Podhorecka et al., 2012). Previous studies revealed little information regarding the functional effects of the 2 *VDR* polymorphisms (Adorini, 2009; Tanaka et al., 2009; Kempińska-Podhorecka et al., 2012). It has been speculated that these *VDR* polymorphisms may be in linkage disequilibrium with unknown real risk variants, and such linkage disequilibrium may vary by ethnicity (Vogel et al., 2002; Tanaka et al., 2009; Kempińska-Podhorecka et al., 2012). Further studies examining the exact molecular mechanism are required to confirm this hypothesis.

There were several limitations to our study. The first limitation is the lack of case-control data adjustment including individual patient information such as age, gender, and lifestyle in this meta-analysis. The second limitation is that the total sample size as well as the subgroup sample sizes used in our meta-analysis were not sufficient to draw final conclusions for the relationship. The third limitation is that the detailed molecular mechanism of the association between the *VDR* polymorphisms and PBC risk remains unknown. Thus, further analysis using adjusted individual data and larger sample sizes is required, and further investigation into the mechanism should be performed.

In conclusion, the results of our meta-analysis of 6 eligible studies (672 cases and 1148 controls in all) indicated that the *VDR Apa*I polymorphism is likely associated with PBC risk, particularly in Asians and that the *VDR Taq*I polymorphism may influence PBC risk in Caucasians. However, no significant association was observed between the *VDR Bsm*I polymorphism and PBC risk. Although there were some limitations, our meta-analysis provides valuable information for studying the relationship between the 3 *VDR* polymorphisms (*Bsm*I, *Apa*I, and *Taq*I) and PBC risk.

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