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Quantitative assessment of the associations between four polymorphisms (*Fok*I, *Apa*I, *Bsm*I, *Taq*I) of vitamin D receptor gene and risk of diabetes mellitus

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Abstract The vitamin D receptor (*VDR*) gene polymorphisms have been suggested to be involved in the development of diabetes mellitus, including type 1 diabetes (T1DM) and type 2 diabetes (T2DM). However, the results have been inconsistent. In this study, we performed a meta-analysis to investigate the associations. Literature was retrieved from PubMed, ISI Web of Science and Chinese databases. Pooled odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated using a random or fixed effect model. 79 studies (*Fok*I: 22 studies; *Bsm*I: 25 studies; *Apa*I: 17 studies; *Taq*I: 15 studies) on T1DM and 44 studies (*Fok*I: 10 studies; *Bsm*I: 10 studies; *Apa*I: 14 studies; *Taq*I: 10 studies) on T2DM were included. The results indicated that *Bsm*I polymorphism was associated with an increased risk of T1DM (B vs. b: OR 1.31, 95 % CI 1.10–1.55, $P = 0.002$), especially in East Asians (B vs. b: OR 2.57, 95 % CI: 1.55–4.24, $P < 0.001$); *Fok*I polymorphism was associated with an increased risk of T2DM (f vs. F: OR 1.30, 95 % CI: 1.17–1.45, $P < 0.001$), especially in East Asians (f vs. F: OR 1.36, 95 % CI: 1.21–1.54, $P < 0.001$). However, no significant association was observed between *Apa*I or *Taq*I polymorphism and diabetes risk with the exception of significant association between *Apa*I polymorphism and T1DM risk in East Asians. Thus, the authors found *Bsm*I polymorphism in the *VDR* gene may increase the risk of T1DM in East Asians and the *Fok*I polymorphism may increase the risk of T2DM in East Asians.

Keywords Vitamin D receptor · Diabetes mellitus · Genetic polymorphism · Meta analysis

Introduction

Diabetes mellitus (DM) is a common chronic disease with high rates of disability and mortality caused by its vascular complications. Type 1 diabetes mellitus (T1DM), accounting for only 5–10 % of diabetes cases worldwide [1], is a T cell mediated autoimmune disease [2] and results from autoimmune destruction of β-cells of the pancreas [1]. Type 2 diabetes mellitus (T2DM), accounting for 90–95 % of those with diabetes, results from a combination of resistance to insulin action and an inadequate compensatory insulin secretory response [1]. Although the two forms of DM can be attributed to environmental factors, such as geography [3], obesity [1], diet and exercise [4], genetic predispositions also play important roles in both developments of DM [1, 3]. The genome-wide association studies (GWAS) have identified many potential loci associated with DM, including SH2B3, ERBB3, PTPN22, IL27, KCNQ1, GLIL3, PEPD, KCNK16 [3, 5, 6]. Candidate gene studies have also revealed some DM loci, including MHC, INS, PTPN2, TCF7L2, PPARGC1A [3, 6–8]. Despite both environmental and genetic factors mentioned above, the complicated mechanisms behind DM remain unclear.

Evidence has suggested that taking vitamin D supplements in early childhood and high vitamin D intake may be inversely associated with risk of incident T1DM and

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T2DM, respectively [9, 10]. Vitamin D possesses the actions of immunity regulation, especially T cell mediated immunity and affects the immune cells with relevance to autoimmunity [11]. High levels of vitamin D can enhance pancreatic β-cell secretion functions and improve insulin resistance [12, 13]. The active form of Vitamin D, 1,25-dihydroxyvitamin D, exerts its bioactivities through the vitamin D receptor (*VDR*), which is an intracellular hormone receptor belonging to the steroid hormone receptor superfamily. Hence, the *VDR* gene may be involved in the pathogenesis and progression of DM including T1DM and T2DM.

At present, *Fok*I (rs10735810), *Bsm*I (rs1544410), *Apa*I (rs7975232) and *Taq*I (rs731236) are the four common single nucleotide polymorphisms (SNPs) in the *VDR* gene that have been most frequently studied [14, 15]. A previous meta-analysis by Guo et al. [16] regarding the associations between the four *VDR* gene polymorphisms and T1DM risk did not identify any genetic variant associated with T1DM. However, since this article was published, sixteen additional papers investigating these associations have been published. In addition, a great number of studies have also investigated the associations between the four *VDR* gene polymorphisms and T2DM risk. However, the results of these studies have been inconsistent.

In this study, a meta-analysis was performed to clarify the associations between the four common polymorphisms (*Fok*I, *Apa*I, *Bsm*I, *Taq*I) in the *VDR* gene and T1DM and T2DM susceptibilities.

Materials and methods

Literature and search strategy

The databases PubMed, ISI Web of Science, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure and Chinese Wanfang Data were searched. The search strategy to identify all possible articles in English or Chinese language involved the use of combination of the following key words: (vitamin D receptor or *VDR*) AND (polymorphism or variation or variant) AND (type 2 diabetes mellitus or NIDDM or type 1 diabetes mellitus or IDDM or diabetes mellitus). If more than one article was published using the same study data, only the study with the largest sample size was included. The literature search was updated on November 11th, 2011.

Inclusion criteria and data extraction

Studies were included if they met the following inclusion criteria: (1) an original article; (2) case–control or cohort study; (3) evaluating the associations of the *VDR* gene polymorphisms (*Fok*I, *Apa*I, *Bsm*I, *Taq*I) with T1DM or T2DM risk; and (4) providing sufficient data for calculation of an odds ratio (OR) with 95 % confidence interval (CI). Studies were excluded if: (1) they were case-only reports or review papers; (2) the cases with other diseases combined such as osteoporosis or coronary heart disease; or (3) the study was based on pedigree data. The following information was extracted from each study: (1) name of first author; (2) year of publication; (3) country of origin; (4) ethnicity of the study population; (5) gender distribution and mean age of subjects in cases and controls; (6) mean age of onset in cases; (7) genotype distributions in cases and controls; and (8) *P* value for the test of Hardy–Weinberg equilibrium (HWE) in controls. Two authors independently assessed the articles for compliance with the inclusion criteria, and disagreement was followed by discussion until consensus was reached.

Quality assessment

The quality of included studies was also independently assessed by two authors using the procedure known as "extended quality score", which was used in the paper by Xu et al. [17] and based on the recommendations of the MOOSE guidelines and other related meta-analytic papers. The procedure with eleven items stems from epidemiological and genetic considerations and the full score is 14 points [17]. Studies were categorized as "high" quality if the score was equal to or greater than 11 points, "medium" if the score was equal to or greater than 7 points and less than 11 points and "poor" if the score was less than 7 points.

Statistical analysis

The associations between *VDR* gene polymorphisms (*Fok*I, *Apa*I, *Bsm*I and *Taq*I) and T1DM or T2DM risk were estimated by calculating pooled ORs with 95 % CIs assuming a multiplicative genetic model (*Fok*I: f vs. F; *Apa*I: a vs. A; *Bsm*I: B vs. b; *Taq*I: t vs. T). The significance of the pooled ORs was determined using *Z* tests ($P < 0.05$ was considered statistically significant). The heterogeneity among studies was evaluated by the *Q*-statistic test and I^2-statistic test [18]. A random- (DerSimonian–Laird method) [19] or fixed- (Mantel–Haenszel method) [20] effects model was used to calculate the pooled ORs in the presence ($P \leq 0.10$) or absence ($P > 0.10$) of heterogeneity. Meta-regression with maximum likelihood estimation was performed to explore the potentially important sources of heterogeneity among studies. Subgroup analysis was also performed based on ethnicity. Sensitivity analysis, removing one study at a time, was performed to evaluate the stability of the results. Begg's

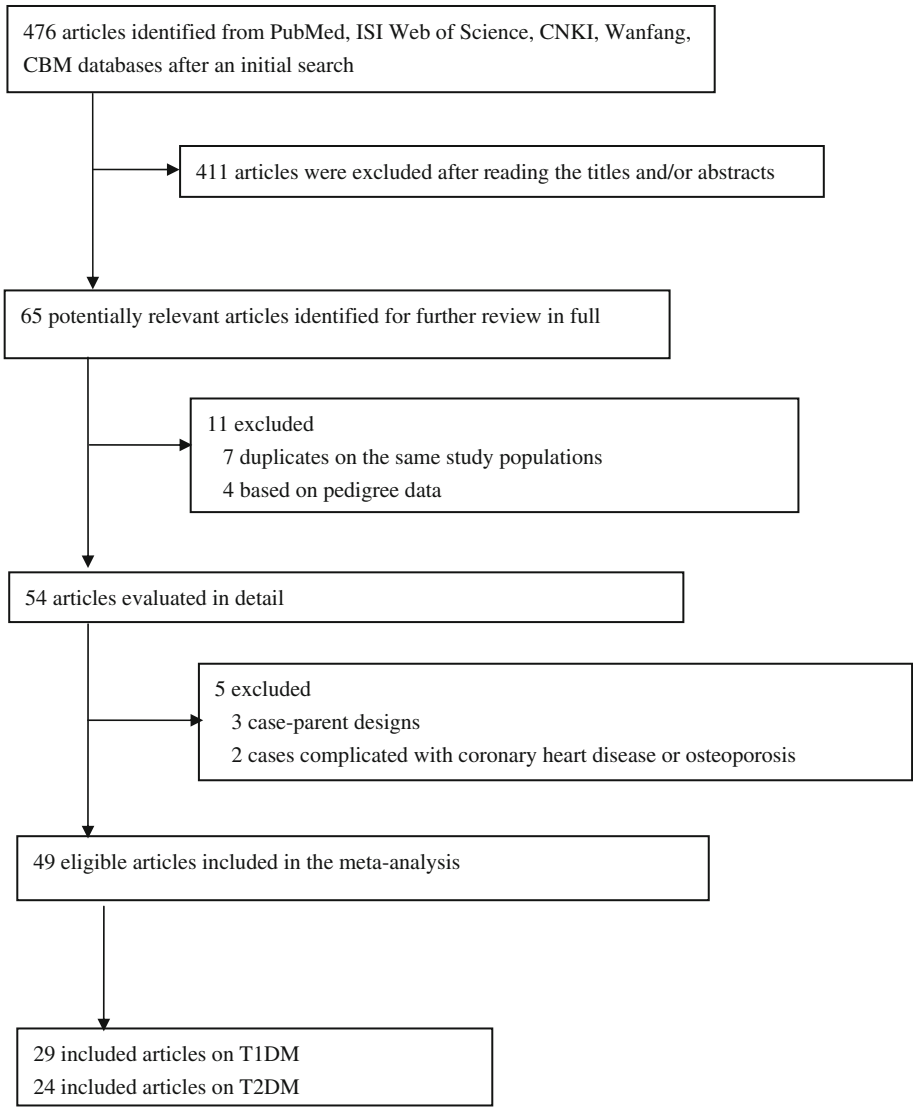

Fig. 1 Selection of articles for inclusion in meta-analysis

funnel plot, a scatter plot of effect against study size, was generated as a visual aid to detect bias or systematic heterogeneity [21]. Publication bias was assessed by Egger's test [22] ($P < 0.05$ was considered statistically significant). Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of the studies

The detailed steps of our literature search are shown in Fig. 1. Based on the search strategy and inclusion criteria, 29 papers were included in the meta-analysis of the associations between polymorphisms in the *VDR* gene and T1DM risk [23–51]. There were 22 studies (2,940 cases and 4,942 controls) for *Fok*I polymorphism, 25 studies (3,854 cases and 6,498 controls) for *Bsm*I polymorphism, 17 studies (2,136 cases and 3,877 controls) for *Apa*I polymorphism, and 15 studies (1,719 cases and 1,843 controls) for *Taq*I polymorphism, respectively. Regarding to the associations between polymorphisms in the *VDR* gene and T2DM risk, 24 papers were included in the meta-analysis [29, 35, 38, 42, 52–71]. For *Fok*I polymorphism, there were 10 studies involving 1,562 cases and 1,461 controls; for *Bsm*I, 10 studies, 1,778 cases and 2,800 controls; for *Apa*I, 14 studies, 1,430 cases and 2,441 controls; for *Taq*I, 10 studies, 1,388 cases and 2,438 controls.

All the included studies were case–control designs. All studies was categorized as "medium" or "high" quality, with the exception that the studies from 3 papers on T1DM

Table 1 Summary ORs and 95 % CIs of the association between VDR gene polymorphism and type 1 diabetes mellitus risk

Locus	Models	Contrasts		Excluded studies (Ref.)	No. of studies	OR	95 % CI	P^a	Statistical model	I^2 (%)	P^b
*Fok*I	f vs. F	Total			22	0.98	0.85–1.13	0.811	Random	74.4	<0.001
		Total[c]		25, 32, 33,37, 47	17	0.97	0.82–1.16	0.766	Random	74.7	<0.001
		Total[d]		25, 26, 32, 33,37, 47	16	1.00	0.83–1.19	0.963	Random	74.6	<0.001
		Ethnicity	Caucasian		10	0.93	0.74–1.17	0.536	Random	76.2	<0.001
			East Asian		4	1.08	0.56–2.06	0.820	Random	88.1	<0.001
			Other		3	1.05	0.85–1.28	0.666	Fixed	0.0	0.955
*Bsm*I	B vs. b	Total			25	1.26	1.10–1.45	0.001	Random	71.2	<0.001
		Total[c]		32, 44,47	21	1.31	1.10–1.55	0.002	Random	74.2	<0.001
		Total[d]		23, 32, 34, 44,47	19	1.31	1.09–1.57	0.004	Random	76.6	<0.001
		Ethnicity	Caucasian		11	1.00	0.90–1.11	0.993	Fixed	36.3	0.108
			East Asian		6	2.57	1.55–4.24	<0.001	Random	79.0	<0.001
			Other		4	1.38	1.17–1.64	<0.001	Fixed	12.5	0.303
*Apa*I	a vs. A	Total			17	0.94	0.84–1.05	0.104	Random	38.8	0.052
		Total[c]		32, 41, 44, 46, 48	12	0.91	0.82–1.02	0.095	Fixed	35.5	0.106
		Total[d]		26, 32, 34, 41, 44, 46, 48	10	0.94	0.84–1.06	0.306	Fixed	27.3	0.193
		Ethnicity	Caucasian		7	0.97	0.80–1.18	0.737	Random	44.7	0.093
			East Asian		4	0.78	0.63–0.96	0.017	Fixed	0.0	0.432
			Other		1	0.88	0.58–1.33	0.543	–	–	–
*Taq*I	t vs. T	Total			15	1.14	0.94–1.38	0.184	Random	61.9	0.001
		Total[c]		27–30, 44, 46, 51	8	1.12	0.96–1.32	0.148	Fixed	0.0	0.445
		Total[d]		26–30, 34, 44, 46, 51	6	1.12	0.94–1.32	0.194	Fixed	23.5	0.257
		Ethnicity	Caucasian		3	0.87	0.65–1.17	0.364	Fixed	0.0	0.448
			East Asian		4	1.22	0.96–1.55	0.102	Fixed	0.0	0.792
			Other		1	1.30	0.96–1.78	0.095	–	–	–

Notes: [a] *P* value for *Z* test

[b] *P* value based on *Q* test for heterogeneity

[c] After the studies deviating from HWE were excluded

[d] After the studies deviating from HWE and those with low quality were excluded

[23, 26, 34] and 2 papers on T2DM [53, 67] were considered as "pool" quality. The characteristics of the studies are listed in Supplementary Tables 1 and 2.

Quantitative synthesis

Type 1 diabetes mellitus

After excluding the studies deviating from HWE in controls, the overall results showed that there was a statistically significant association between *Bsm*I polymorphism and an increased risk of T1DM (B vs. b: OR 1.31, 95 % CI 1.10–1.55, $P = 0.002$), with evidence of heterogeneity among studies ($I^2 = 74.2$ %, $P < 0.001$) (Table 1; Fig. 2). For the other three polymorphisms, no significant association was found in the overall population after the studies deviating from HWE in controls were excluded. For *Fok*I polymorphism, the pooled summary OR was 0.97 (95 % CI: 0.82–1.16, $P = 0.766$), with evidence of heterogeneity among studies ($I^2 = 74.7$ %, $P < 0.001$); for *Apa*I polymorphism, the pooled summary OR was 0.91 (95 % CI 0.82–1.02, $P = 0.095$), with moderate heterogeneity between studies ($I^2 = 35.5$ %, $P = 0.106$); for *Taq*I polymorphism, the pooled summary OR was 1.12 (95 % CI: 0.96–1.32, $P = 0.148$), and there was no evidence of heterogeneity between studies ($I^2 = 0.0$ %, $P = 0.445$) (Table 1; Supplementary Figs. 1–3). Further subgroup analyses by ethnicity showed that the effect sizes were statistically significant in East Asians for *Bsm*I (B vs. b: OR 2.57, 95 % CI: 1.55–4.24, $P < 0.001$) and *Apa*I polymorphisms (a vs. A: OR 0.78, 95 % CI: 0.63–0.96, $P = 0.017$) (Table 1).

Type 2 diabetes mellitus

After excluding the study deviating from HWE in controls, the overall result showed that there was a statistically significant association between *Fok*I polymorphism and an increased risk of T2DM (f vs. F: OR 1.30, 95 % CI:

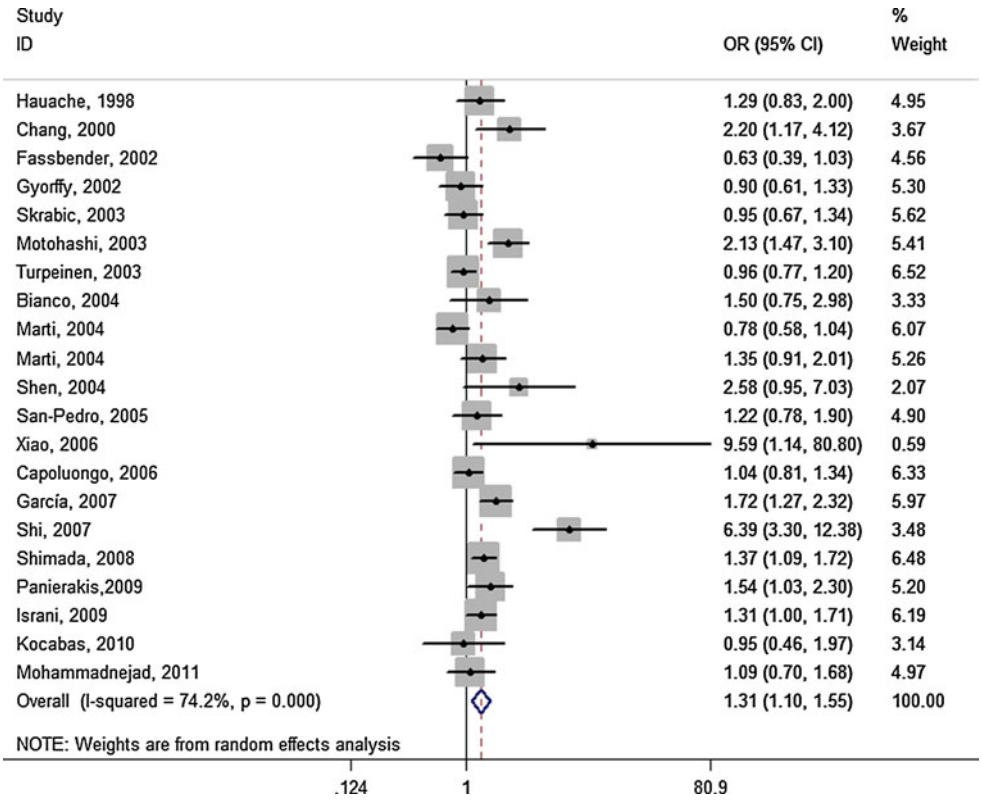

Fig. 2 Meta-analysis of the association between *Bsm*I polymorphism in the *VDR* gene and type 1 diabetes (B vs. b)

1.17–1.45, $P < 0.001$), with moderate heterogeneity between studies ($I^2 = 36.8$ %, $P = 0.124$) (Table 2; Fig. 3). For *Bsm*I polymorphism, a marginally significant association with T2DM risk was found after the study deviating from HWE in controls was excluded (B vs. b: OR 1.49, 95 % CI: 1.03–2.15, $P = 0.033$), with evidence of heterogeneity between studies ($I^2 = 84.8$ %, $P < 0.001$). For *Apa*I polymorphism, the pooled summary OR was 1.00 (95 % CI: 0.88–1.13, $P = 0.978$), with no sign of heterogeneity between studies ($I^2 = 0$ %, $P = 0.476$). For *Taq*I polymorphism, the pooled summary OR was 0.92 (95 % CI: 0.72–1.18, $P = 0.526$), with evidence of heterogeneity between studies ($I^2 = 60.8$ %, $P = 0.018$) (Table 2; Supplementary Figs. 4–6). Further subgroup analyses by ethnicity showed that the effect sizes were statistically significant in East Asians for *Fok*I (f vs. F: OR 1.36, 95 % CI: 1.21–1.54, $P < 0.001$) and *Bsm*I polymorphisms (B vs. b: OR 2.60, 95 % CI: 1.82–3.72, $P < 0.001$) (Table 2).

Sensitivity analysis

A sensitivity analysis was performed by excluding one study at a time. Results for the association between *Bsm*I polymorphism and T1DM risk remained statistically significant, with the ORs with 95 % CIs ranging from 1.22 (1.06–1.41) to 1.35 (1.14–1.60). In addition, the positive association between *Fok*I polymorphism and T2DM risk was also confirmed by the sensitivity analysis, with the ORs with 95 % CIs ranging from 1.26 (1.13–1.41) to 1.36 (1.21–1.53). However, the sensitivity analysis indicated that the significant association between *Bsm*I polymorphism and T2DM risk was not robust (data not shown).

Sources of heterogeneity

The meta-regression was conducted with the covariates publication year, ethnicity, latitude of the city or region, sex frequency of cases and controls, mean age of cases and controls, age of onset in cases and BMI of cases and controls. However, no covariate was identified as a potential source of heterogeneity among studies for any comparison.

Potential publication bias

Using Egger's test, no publication bias could be detected for studies published on the associations of the above-mentioned polymorphisms in the *VDR* gene with DM risk (T1DM: *Fok*I, $P = 0.653$; *Bsm*I, $P = 0.052$; *Apa*I, $P = 0.719$; *Taq*I, $P = 0.367$; T2DM: *Fok*I, $P = 0.460$; *Bsm*I, $P = 0.421$; *Apa*I, $P = 0.721$; *Taq*I, $P = 0.269$).

Table 2 Summary ORs and 95 % CIs of the association between *VDR* gene polymorphism and type 2 diabetes mellitus risk

Locus	Models	Contrasts		Excluded studies (Ref.)	No. of studies	OR	95 % CI	P^a	Statistical model	I^2 (%)	P^b
*Fok*I	f vs. F	Total			10	1.30	1.18–1.45	<0.001	Fixed	29.6	0.173
		Total[c]		65	9	1.30	1.17–1.45	<0.001	Fixed	36.8	0.124
		Ethnicity	Caucasian		1	1.08	0.85–1.37	0.549	–	–	–
			East Asian		8	1.36	1.21–1.54	<0.001	Fixed	28.2	0.203
*Bsm*I	B vs. b	Total			14	1.41	1.04–1.92	0.028	Random	83.8	<0.001
		Total[c]		55	13	1.49	1.03–2.15	0.033	Random	84.8	<0.001
		Total[d]		53, 55, 67	11	1.52	1.01–2.28	0.043	Random	86.3	<0.001
		Ethnicity	Caucasian		3	0.90	0.75–1.07	0.228	Fixed	0.0	0.684
			East Asian		8	2.60	1.82–3.72	<0.001	Random	46.8	0.068
			Other		2	0.55	0.24–1.25	0.154	Random	78.8	0.030
*Apa*I	a vs. A	Total			10	1.03	0.98–1.07	0.305	Fixed	17.8	0.279
		Total[c]		55	9	1.00	0.88–1.13	0.978	Fixed	0.0	0.476
		Ethnicity	Caucasian		3	0.98	0.83–1.16	0.816	Fixed	18.8	0.292
			East Asian		4	1.01	0.80–1.27	0.957	Fixed	23.7	0.269
			Other		2	1.04	0.78–1.38	0.790	Fixed	5.2	0.304
*Taq*I	t vs. T	Total			10	0.96	0.81–1.13	0.592	Random	42.9	0.072
		Total[c]		29, 55, 69	7	0.92	0.72–1.18	0.526	Random	60.8	0.018
		Ethnicity	Caucasian		3	0.91	0.76–1.07	0.257	Fixed	0.0	0.438
			East Asian		1	0.76	0.34–1.69	0.593	–	–	–
			Other		3	0.88	0.44–1.75	0.710	Random	84.4	0.002

Notes: [a] *P* value for *Z* test

[b] *P* value based on *Q* test for heterogeneity

[c] After the studies deviating from HWE were excluded

[d] After the studies deviating from HWE and those with low quality were excluded

Discussion

The vitamin D has important biological functions, such as modulating immunity system, influencing insulin secretion and improving insulin resistance [11, 13], which are involved in the etiology of DM and more likely to be influenced by *VDR* gene polymorphisms. Given the controversial results from published individual studies with small sample sizes, we performed a meta-analysis to clarify the association between the *VDR* gene polymorphisms and susceptibility to diabetes mellitus.

To our knowledge, the present study is the first meta-analysis of the association between *VDR* gene polymorphisms (*Fok*I, *Apa*I, *Bsm*I, *Taq*I) and risk of T2DM. In addition, the included sample size in our meta-analysis is more than double that of the meta-analysis on T1DM risk by Guo et al. [16]. Our meta-analysis suggests that *Fok*I polymorphism in the *VDR* gene is significantly associated with T2DM risk, especially in East Asians, but not with T1DM risk; *Bsm*I polymorphism in the *VDR* gene was associated with T1DM risk, especially in East Asians, but not with T2DM risk in the overall population, except in East Asians. However, no significant association was found between *Apa*I or *Taq*I polymorphism and any type of DM with the exception of significant association between *Apa*I polymorphism and T1DM risk in East Asians.

The human *VDR* gene, with a resolution of >100 kb, is located on chromosome 12q12–q14. So far, a number of polymorphisms have been found in and around exons 1f–1c in the 5′ promoter area, in and around the eight protein-coding exons 2–9, and in the 3′ untranslated region (UTR) of the gene [15]. However, among these loci, the *Fok*I polymorphism (ATG–ACG) located in the exon 2 of the gene is the only known locus affecting the structure of the *VDR* protein produced. The f allele encodes a 427 amino acid protein while the F allele encodes a 424 amino acid protein [15, 72, 73]. The shorter *VDR* protein variant seem to function more effectively and further increase its capacity of binding 1,25-dihydroxyvitamin D [74], and the relatively higher level of vitamin D, in turn, can reduce the risk of T2DM by enhancing pancreatic β-cell secretion function and improve insulin resistance [12, 13]. This biological mechanism could explain the association

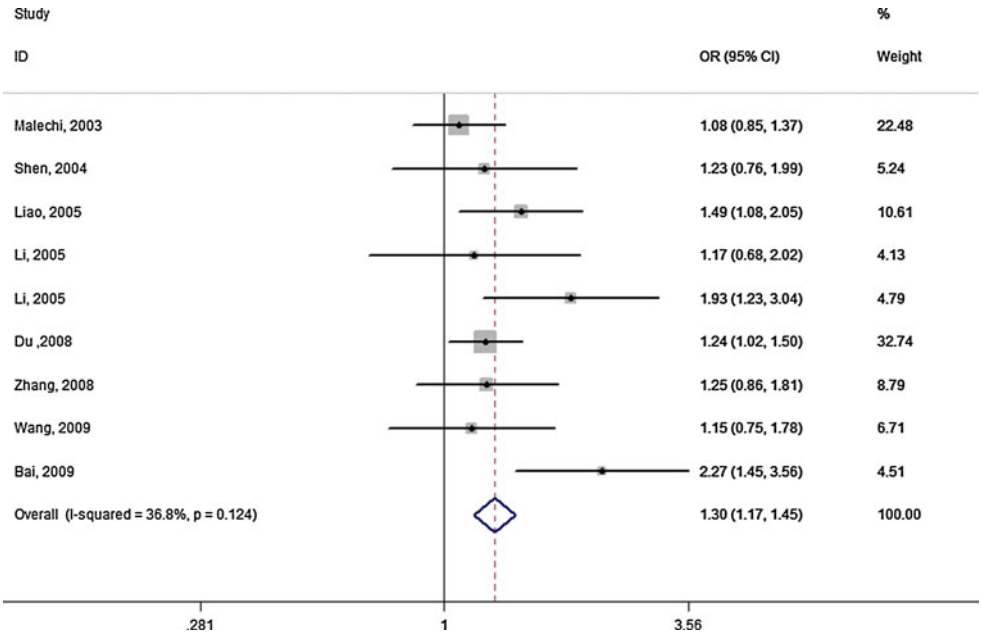

Fig. 3 Meta-analysis of the association between *Fok*I polymorphism in the *VDR* gene and type 2 diabetes (f vs. F)

between the f allele of *Fok*I polymorphism and susceptibility to T2DM.

It has been suggested that the *Taq*I polymorphism is a silent mutation despite being located in exon 9, and both *Bsm*I and *Apa*I are located in the intron between extons 8 and 9 and do not alter the amount of the *VDR* protein, structure or function [15]. However, in our meta-analysis, a significant association was suggested between *Bsm*I polymorphism and T1DM risk in the overall population especially in East Asians while the association between *Bsm*I polymorphism and T2DM risk was only found in East Asians. So far, the potential mechanism underlying the association of *Bsm*I polymorphism with DM risk remains unclear. The polyA variable number of tandem repeat (VNTR) in the 3′ UTR may be the real effect variation predisposing to the disease, which is in strong linkage disequilibrium (LD) with *Bsm*I polymorphism and related to *VDR* messenger RNA stability [15, 75]. In addition, it is possible that the *Bsm*I polymorphism in the *VDR* gene contributes to T-helper 1 response involved in the development of T1DM because of higher levels of interferon-gamma (IFN-γ) produced by peripheral blood mononuclear cells of T1DM patients with BB genotype [45, 46]. Some evidence suggests that the *Bsm*I polymorphism may influence gene transcription, thereby increasing the level of parathormone and osteocalcin and reducing the level of intestinal calcium absorption. These factors, in turn, increase intracellular calcium in adipocytes, enhance lipogenesis and increase demand for insulin, leading to a higher incidence of insulin resistance and T2DM [76]. Further research is required to probe into the actual action of the *Bsm*I polymorphism.

Several limitations in the present meta-analysis should be noted. First, the pooled results were based on unadjusted estimates and therefore potential covariates were not controlled for, including age, gender, vitamin D status varying with ultraviolet level and dietary intake, as well as factors such as physical activity and BMI. Second, although there was heterogeneity among studies in some comparisons in our meta-analysis, no covariate was identified as a potential source of heterogeneity between studies by meta-regression. Therefore, other unknown confounding factors may help explain the between-study heterogeneity. Third, despite gene–gene and gene-environment interactions involved in the pathogenesis of DM, these effects were not assessed in our meta-analysis due to insufficient data from the included studies. Finally, the results of our meta-analysis should be interpreted with caution because the sample size was reduced after the subgroup analysis was performed. However, as a useful statistical tool, meta-analysis allows pooling data from individual studies, thereby undoubtedly increasing the statistical power and the precision of effect estimates.

In conclusion, our meta-analysis suggests that the *Bsm*I polymorphism in the *VDR* gene is significantly associated with T1DM risk in East Asians and the *Fok*I polymorphism is significantly associated with T2DM risk in East Asians. However, future studies considering gene–gene and gene-environment interactions are needed to investigate these associations. Furthermore, more in depth research is also required to clarify the mechanisms behind the associations of the *VDR* polymorphisms and DM.

Conflict of interest The authors declare no conflict of interest.

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