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Research article

Vitamin D receptor polymorphisms and the susceptibility of Parkinson's disease

Xiong Wang[a], Na Shen[a], Yanjun Lu[a], Kun Tan[b,*]

[a] Department of Laboratory Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[b] Department of Infection Control, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China

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ABSTRACT

Epidemiological evidence concerning the association between vitamin D receptor (VDR) polymorphisms, including rs2228570, rs731236, rs7975232, rs1544410 and Parkinson's disease (PD) risk is inconsistent. A meta-analysis was performed to evaluate these associations via searching PubMed and EMBASE databases up to Jan 4, 2019. Odds ratio (OR) with 95% confidence interval (CI) were applied to assess the strength of these associations. 6 studies with 1391 PD cases and 1570 controls for rs2228570, 7 studies with 1881 PD cases and 2135 controls for rs731236, 5 studies with 1298 PD cases and 1536 controls for rs7975232, and 6 studies with 932 PD cases and 1377 controls for rs1544410 were included in this meta-analysis. Significant associations between rs2228570 and PD risk were found in allelic, dominant, and additive models but not in recessive model. Stratified study revealed that rs2228570 was associated with PD susceptibility in Asian population, while no significant association was observed in Caucasian population. Sensitivity analysis showed stable results for rs2228570 and no publication bias existed. Rs731236 was associated with increased PD risk in dominant model, however, this result was unstable. No significant association was found between rs7975232 or rs1544410 and PD.

1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder. The pathogenic characteristics includes the presence of Lewy bodies and the loss of dopaminergic cells in the substantia nigra, but the underling mechanisms remain unclear. The motor symptom of PD includes tremor, rigidity, flexed posture, bradykinesia, and postural instability [11]. Environmental and genetic factors may contribute to the pathogenesis of PD [19].

Vitamin D deficiency was associated with increased PD risk [17]. The vitamin D receptor (VDR) acts as mediator of vitamin D's biological actions. VDR is enriched in dopaminergic neurons within the substantia nigra, and knockout of *VDR* gene resulted motor impairments [2]. Several studies explored the association between *VDR* polymorphisms and PD susceptibility including rs2228570, rs731236, rs7975232, and rs1544410 [3,20]. However, these results were controversial [4–7,27,28]. Three published meta-analyses [12,13,20] evaluated these associations, however, all the three results were based on limited studies.

With the increasing evidence, we performed this meta-analysis to investigate the association between VDR polymorphisms including rs2228570, rs731236, rs7975232, rs1544410 and PD susceptibility to provide more reliable analysis.

2. Materials and methods

2.1. Literature search

The literary searches in PubMed and EMBASE databases up to Jan 4, 2019 including the following keywords: 'vitamin D receptor OR *VDR*', 'polymorphism OR variant OR mutation', and 'Parkinson's disease OR PD'.

2.2. Inclusion and exclusion criteria

The inclusion criteria include: Case-control study with sufficient genotype information investigating *VDR* rs2228570 (FokI), rs731236 (TaqI), rs7975232 (ApaI) or rs1544410 (Bsm) polymorphism and PD risk. Studies exclusion criteria include: (1) Reviews, case reports, and editorials; (2) Family-based study; (3) Study with insufficient genotype information; (4) Genotype distribution of controls not in Hardy-Weinberg equilibrium (HWE).

* Corresponding author.
E-mail address: tankun88888@126.com (K. Tan).

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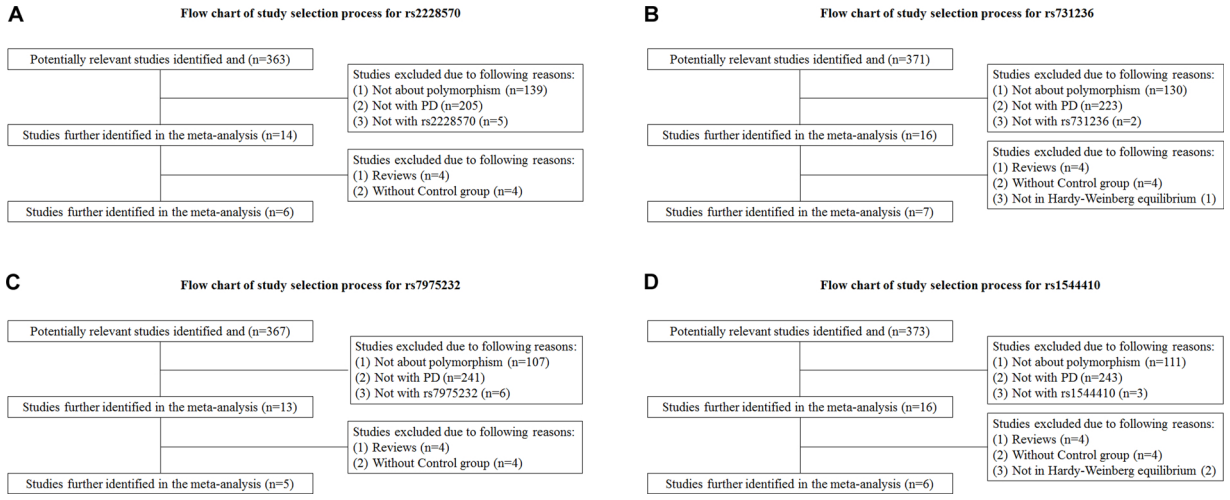

Fig. 1. Flow chart of study selection process in the current meta-analysis. (A) rs2228570. (B) rs731236. (C) rs7975232. (D) rs1544410.

Table 1
Characteristics of the included studies in this meta-analysis.

SNP	Author	Year	Country	Ethnicity	Method	Age		Sample size	
						Case	Control	Case	Control
rs2228570	Tanaka K	2017	Japan	Asian	TaqMan	68.4 ± 8.7	66.6 ± 8.5	229	357
	Gezen-Ak D	2016	Turkey	Caucasian	TaqMan	61.7 ± 11.4	64.6 ± 10.3	382	237
	Kang SY	2016	Korea	Asian	TaqMan	69.5 ± 9.7	66.7 ± 8.8	137	163
	Gatto NM	2015	USA	Caucasian	TaqMan	70.9 ± 10.5	67.6 ± 12.0	283	422
	Török R	2013	Hungary	Caucasian	PCR-RFLP	66.4 ± 9.3	64.0 ± 8.2	100	109
	Han X	2012	China	Asian	PCR-RFLP	70.9 ± 6.1	69.4 ± 9.7	260	282
rs731236	Tanaka K	2017	Japan	Asian	TaqMan	68.4 ± 8.7	66.6 ± 8.5	229	357
	Gezen-Ak D	2016	Turkey	Caucasian	TaqMan	61.7 ± 11.4	64.6 ± 10.3	381	240
	Gatto NM	2015	USA	Caucasian	TaqMan	70.9 ± 10.5	67.6 ± 12.0	282	421
	Petersen MS	2014	Danmark	Caucasian	TaqMan	74.5 ± 9.9	75.0 ± 9.9	121	234
	Török R	2013	Hungary	Caucasian	PCR-RFLP	66.4 ± 9.3	64.0 ± 8.2	100	109
	Lv Z	2013	China	Asian	PCR-RFLP	54.7 ± 11.9	52.0 ± 17.9	483	489
	Liu HX	2013	China	Asian	PCR-RFLP	66.18 ± 10.77	71.8 ± 6.1	285	285
rs7975232	Tanaka K	2017	Japan	Asian	TaqMan	68.4 ± 8.7	66.6 ± 8.5	229	357
	Gezen-Ak D	2016	Turkey	Caucasian	TaqMan	61.7 ± 11.4	64.6 ± 10.3	381	241
	Gatto NM	2015	USA	Caucasian	TaqMan	70.9 ± 10.5	67.6 ± 12.0	282	419
	Petersen MS	2014	Danmark	Caucasian	TaqMan	74.5 ± 9.9	75.0 ± 9.9	121	234
	Liu HX	2013	China	Asian	PCR-RFLP	66.18 ± 10.77	71.8 ± 6.1	285	285
rs1544410	Tanaka K	2017	Japan	Asian	TaqMan	68.4 ± 8.7	66.6 ± 8.5	229	357
	Kang SY	2016	Korea	Asian	TaqMan	69.5 ± 9.7	66.7 ± 8.8	137	163
	Petersen MS	2014	Danmark	Caucasian	TaqMan	74.5 ± 9.9	75.0 ± 9.9	121	235
	Török R	2013	Hungary	Caucasian	PCR-RFLP	66.4 ± 9.3	64.0 ± 8.2	100	109
	Han X	2012	China	Asian	PCR-RFLP	70.9 ± 6.1	69.4 ± 9.7	260	282
	Kim JS	2005	Korea	Asian	PCR-RFLP	64.55 ± 8.86	62.05 ± 10.44	85	231

2.3. Data extraction

First author's surname, published year, Country, ethnicity, genotyping method, age, male ratio, sample size, and genotype information were extracted.

2.4. Statistical analysis

All data were analyzed with Stata 12.0 software (Stata Coporation, TX, USA). The strength of this association was evaluated by pooled OR and 95% CI in four genetic models, including allelic, dominant, recessive, and additive models. The fixed-effect model was adopted if $P_Q > 0.1$ or $I^2 < 50\%$. Alternatively, the random-effect model was applied. The stability of the results was assessed by sensitivity analysis. Publication bias was determined by Begger's and Egger's tests. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Characteristics of eligible studies

The study selection process was shown in Fig. 1. 4 reviews [12,13,20,29], and 4 studies without sufficient genotype information [1,3,25,26] were excluded. Eventually, 6 studies with 1391 PD cases

Table 2
Genotype frequencies of VDR SNPs in the included studies.

SNP	Author	Case			Control			MAF		HWE
		FF	Ff	ff	FF	Ff	ff	Case	Control	
rs2228570	Tanaka K	108	98	23	141	169	47	31.44%	36.83%	0.744
	Gezen-Ak D	181	164	37	105	107	25	31.15%	33.12%	0.769
	Kang SY	46	63	28	48	79	36	43.43%	46.32%	0.746
	Gatto NM	109	126	48	153	203	66	39.22%	39.69%	0.922
	Török R	42	48	10	35	49	25	34.00%	45.41%	0.33
	Han X	114	124	22	109	126	47	32.31%	39.01%	0.306
rs731236	Tanaka K	178	47	4	284	67	6	12.01%	11.06%	0.381
	Gezen-Ak D	154	182	45	109	98	33	35.70%	34.17%	0.153
	Gatto NM	77	162	43	153	213	55	43.97%	38.36%	0.152
	Petersen MS	47	54	20	81	119	34	38.84%	39.96%	0.36
	Török R	35	48	17	47	46	16	41.00%	35.78%	0.394
	Lv Z	437	46	0	446	52	0	4.76%	5.32%	0.219
	Liu HX	252	33	0	255	30	0	5.79%	5.26%	0.348
rs7975232	Tanaka K	18	102	109	32	156	169	69.87%	69.19%	0.638
	Gezen-Ak D	130	194	57	101	115	25	40.42%	34.23%	0.354
	Gatto NM	78	158	46	105	210	104	44.33%	49.88%	0.961
	Petersen MS	34	62	25	58	120	56	46.28%	49.57%	0.694
	Liu HX	130	135	20	149	112	24	30.70%	28.07%	0.651
rs1544410	Tanaka K	178	45	6	291	60	6	12.45%	10.08%	0.167
	Kang SY	123	13	1	145	17	1	5.47%	5.83%	0.524
	Petersen MS	48	53	20	84	117	34	38.43%	39.36%	0.51
	Török R	27	49	24	27	57	25	48.50%	49.08%	0.629
	Han X	222	34	4	244	36	2	8.08%	7.09%	0.599
	Kim JS	72	11	2	168	60	3	8.82%	14.29%	0.357

Note: For rs2228570, FF was GG, Ff was GA, ff was AA. For rs731236, FF was AA, Ff was AG, ff was GG. For rs7975232, FF was AA, Ff was AC, ff was CC. For rs1544410, FF was CC, Ff was CT, ff was TT.

Table 3
Meta-analysis of VDR polymorphisms and risk of PD.

SNP	Genetic comparison	P_Q	I^2	OR	95% CI	P_Z
rs2228570	Overall					
	A vs G	0.315	15.5%	0.843	0.757, 0.939	0.002
	AA + GA vs GG	0.890	0.0%	0.819	0.705, 0.951	0.009
	AA vs GA + GG	0.065	51.9%	0.739	0.537, 1.017	0.063
	AA vs GG	0.118	43.1%	0.704	0.558, 0.887	0.003
	Asian					
	A vs G	0.698	0.0%	0.793	0.679, 0.926	0.003
	AA + GA vs GG	0.891	0.0%	0.778	0.628, 0.965	0.022
	AA vs GA + GG	0.213	35.3%	0.673	0.457, 0.992	0.046
	AA vs GG	0.382	0.0%	0.603	0.430, 0.846	0.003
	Caucasian					
	A vs G	0.133	50.3%	0.864	0.690, 1.082	0.203
	AA + GA vs GG	0.591	0.0%	0.858	0.696, 1.057	0.151
	AA vs GA + GG	0.058	64.9%	0.788	0.457, 1.358	0.391
	AA vs GG	0.075	61.3%	0.735	0.422, 1.283	0.279
rs731236	Overall					
	G vs A	0.735	0.0%	1.110	0.987, 1.248	0.082
	GG + AG vs AA	0.355	9.7%	1.167	1.001, 1.361	0.048
	GG vs AG + AA	0.846	0.0%	1.068	0.823, 1.385	0.620
	GG vs AA	0.690	0.0%	1.205	0.909, 1.598	0.195
rs7975232	Overall					
	C vs A	0.031	62.3%	1.015	0.845, 1.220	0.872
	CC + AC vs AA	0.217	30.7%	1.127	0.949, 1.339	0.174
	CC vs AC + AA	0.051	57.6%	0.901	0.658, 1.234	0.516
	CC vs AA	0.000	98.6%	0.513	0.059, 4.477	0.546
rs1544410	Overall					
	T vs C	0.378	6.0%	0.999	0.842, 1.185	0.989
	TT + CT vs CC	0.251	24.4%	0.937	0.758, 1.159	0.550
	TT vs CT + CC	0.960	0.0%	1.232	0.839, 1.808	0.288
	TT vs CC	0.931	0.0%	1.157	0.757, 1.766	0.501

and 1570 controls for rs2228570, 7 studies with 1881 PD cases and 2135 controls for rs731236, 5 studies with 1298 PD cases and 1536 controls for rs7975232, and 6 studies with 932 PD cases and 1377 controls for rs1544410 were included in this meta-analysis [4–6,9,14,18,22,27,28]. Characteristics and genotype information of included studies were summarized in Tables 1 and 2.

3.2. Meta-analysis of the VDR polymorphisms and the susceptibility of PD

Heterogeneity was found in the recessive genetic model for rs2228570, allelic, recessive, and additive models for rs7975232, while no obvious heterogeneity was found for rs731236 or rs1544410 (Table 3). The OR and 95% CI were calculated according to the values of P_Q and I^2 (Fig. 2, Table 3).

VDR rs2228570 was significantly associated with decreased PD risk in the allelic, dominant, and additive models (A vs G: OR = 0.843, 95% CI: 0.757-0.939, P = 0.002; AA + GA vs GG: OR = 0.819, 95% CI: 0.705-0.951, P = 0.009; AA vs GG: OR = 0.704, 95% CI: 0.558, 0.887, P = 0.003) but not in recessive model (AA vs GA + GG: OR = 0.739, 95% CI: 0.537–1.017, P = 0.063). Stratified analysis showed that *VDR* rs2228570 was associated with decreased PD susceptibility in all four models in Asian population, while no significant association was observed in none of the four models in Caucasian population (Table 3).

VDR rs731236 was significantly associated with increased risk of PD in dominant model (GG + AG vs AA: OR = 1.167, 95% CI: 1.001–1.361, P = 0.048). No significant association between rs7975232 or rs1544410 and PD risk was found in any genetic model (Table 3).

Fig. 2. Forest plots for meta-analysis of VDR polymorphisms and risk of PD. (A) rs2228570. (B) rs731236. (C) rs7975232. (D) rs1544410.

3.3. Sensitivity and publication bias

Sensitivity analysis showed stable results for rs2228570 and rs1544410. For rs731236, increased risk of PD was found in dominant model, however, this result was unstable. After omission of study by Tanaka K, Gezen-Ak D, Gatto NM, Török R or Liu HX, on remarkable association was found. The results for rs7975232 were unstable either (Fig. 3). No significant publication bias existed (Table 4), indicating reliable results for rs2228570 and rs1544410 in this meta-analysis.

4. Discussion

Vitamin D is an essential secosteroid involved the regulation of brain activity. Several studies reported the association between serum vitamin D level and the risk of PD, but the conclusion was ambiguous [15]. Sleeman I found that PD patients had lower serum vitamin D level than age-matched controls [24]. Ozturk EA also indicated the osteoporosis risk in PD due to the low vitamin D level [21]. Kim JE observed olfactory dysfunction in PD patients, and these patients showed low serum vitamin D level. Vitamin D level was suspected to be an independent factor of olfactory dysfunction in PD [8]. Luthra NS characterized vitamin D supplementation and the clinical outcome in early PD within a large cohort of 1741 participants. They found that vitamin D supplementation did not affect PD progression [16], which was consistent with other studies by Larsson SC [10]. Further studies with larger sample size and different ethnic population may be needed to accurately evaluate this association between vitamin D level and PD risk.

VDR rs2228570 polymorphism A allele was associated with decreased risk of PD. Significant association between rs2228570 and decreased PD risk was found in dominant and addictive models but not in recessive model. Moreover, rs2228570 was associated with decreased PD risk in Asian population in all four genetic models, while no remarkable association was observed in Caucasian population.

3 recent meta-analysis studies investigated the association between *VDR* rs2228570 polymorphism and PD [12,13,20], however, their results were duplicated and based on only 2 studies. Han X reported that the frequency of rs2228570/G allele was significantly increased in PD group in Chinese population [6]. Török R also reported similar results in Hungarians [28]. Gezen-Ak D found that A allele carriers for *VDR* rs2228570 were more frequent in patients with advanced-stage PD [5]. However, no significant association was reported by Gatto NM and Kang SY [4,7]. Tanaka K found significant inverse association between *VDR* rs2228570 and PD risk under the additive genetic model, but it fell below significance after adjustment for multiple comparisons [27].

Some factors may contribute to the differences among studies for rs2228570. Only in the study by Tanaka K, the male ratio was strictly matched between PD (38.4%) and Control (38.7%) groups. The male

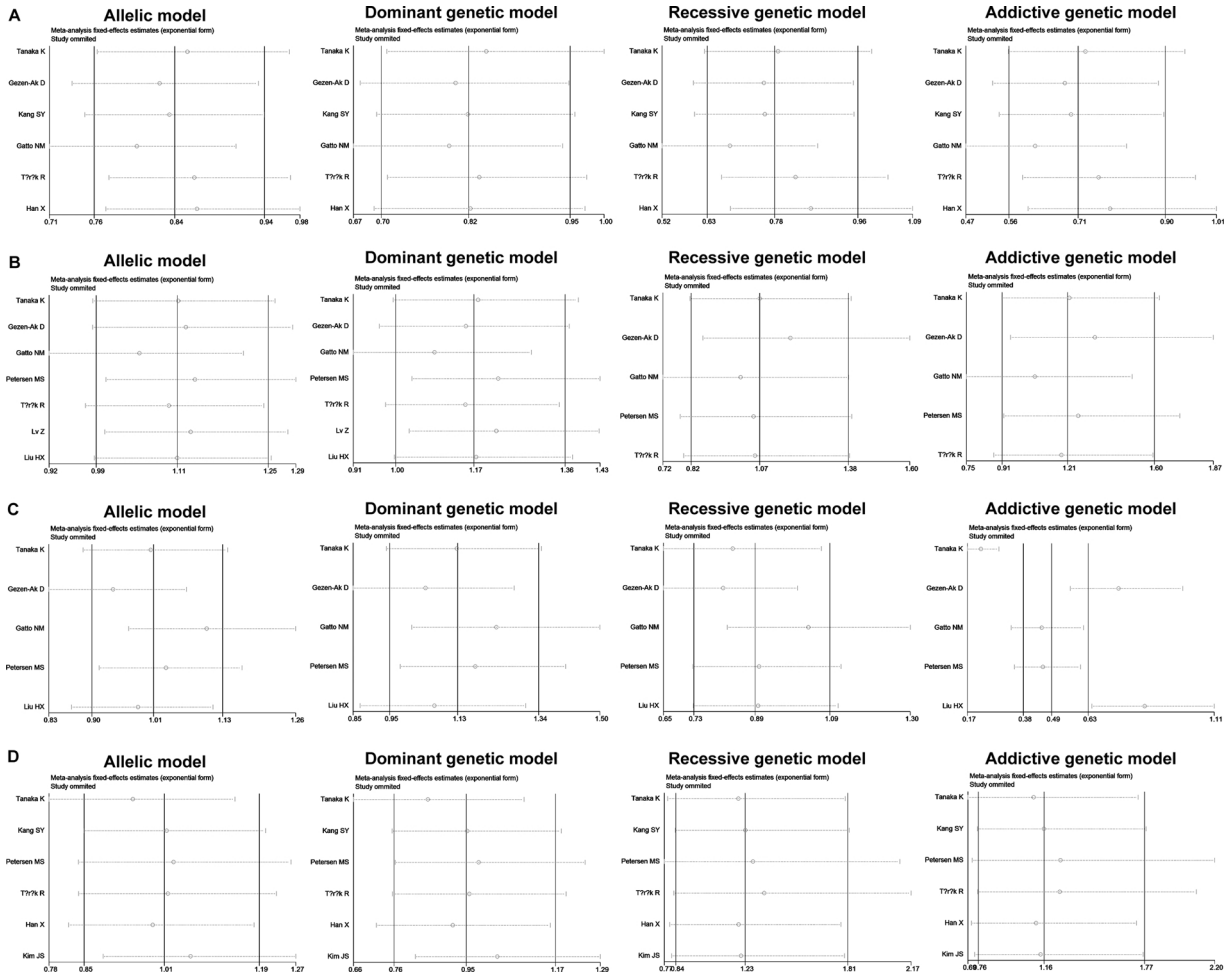

Fig. 3. Sensitivity analysis for meta-analysis of VDR polymorphisms and risk of PD. (A) rs2228570. (B) rs731236. (C) rs7975232. (D) rs1544410.

ratio in PD and Control groups in the studies by Kang SY, Gatto NM, Török R, and Han X were 43.80% vs 55.8%, 55.80% vs 50.1%, 44% vs 49%, 63.87% vs 56.14% respectively. In an exploratory study by Savica R indicated that risk factors for PD differed in men and women [23]. Moreover, the classification of early-onset PD (EOPD) and late-onset PD patients (LOPD) were different among studies. The cut-off value of age was 50 years old by Han X and Gezen-Ak D, while this value was 60 years old in the study by Török R and Kang SY. In the studies by Gatto NM and Gezen-Ak D, some PD cases with family history were included. Furthermore, 25-OH vitamin D_3 level was not detected and adjusted in all studies. Only in the study by Kang SY, the P value was adjusted by 25-OH vitamin D_3 level. Ethnicity may also contribute to this difference. Significant association was only found in Asian population but not Caucasian population. Finally, the genotyping method maybe also need attention. Significant association was found by Han X and Török R, and PCR-RFLP was used in the two studies. In the remaining four studies without significant association was detected by TaqMan. The differences between Asian and Caucasian populations may be caused by ethnicity. The male ratio, sample size, mean age, and MAF between Asian and Caucasian populations were similar as showed in the included 6 studies for rs2228570.

For rs731236, only significant association was found in dominant model. However, this result was unstable, after omitting any of the studies by Tanaka K, Gezen-Ak D, Gatto NM, Török R or Liu HX, indicated by sensitivity analysis. Among the included 7 studies for rs731236, only the study by Gatto NM showed positive association. For rs7975232 and rs1544410, no significant association was found in any genetic model. Only 5 studies were included for rs7975232. Only the study by Kim JS reported positive association for rs1544410. Sensitivity analysis showed stable result for rs1544410.

Some limitations still existed in the current meta-analysis. First, the sample size was still small. Second, the stratified analysis was performed only by ethnicity, without considering other factors including 25-OH vitamin D_3 level, gender, EOPD/LOPD. Third, only 3 studies were analyzed for Asian and Caucasian population respectively in subgroup analysis. All of these limitations may lead to bias in our results.

In conclusion, our meta-analysis suggested that *VDR* rs2228570 was significantly associated with PD in Asian population but not Caucasian population. *VDR* rs1544410 was not associated with PD. However, future studies with larger sample size, gene-gene and gene-environment interaction, different ethnic populations will be needed to provide a more reliable evaluation of associations between *VDR* polymorphisms and the susceptibility of PD.

Conflict of interest

The authors have no conflict of interest to declare.

Table 4
Publication bias analysis of the meta-analysis.

		Test	t (95% CI)	P value
rs2228570	A vs G	Begg's Test		0.060
		Egger's test	−1.67 (−9.266, 2.297)	0.170
	AA + GA vs GG	Begg's Test		0.133
		Egger's test	−1.42 (−4.492, 1.448)	0.228
	AA vs GA + GG	Begg's Test		0.260
		Egger's test	−2.36 (−11.912, 0.959)	0.077
	AA vs GG	Begg's Test		0.133
		Egger's test	−2.19 (−11.022, 1.289)	0.093
rs731236	G vs A	Begg's Test		0.764
		Egger's test	−0.97 (−3.728, 1.687)	0.377
	GG + AG vs AA	Begg's Test		0.764
		Egger's test	−0.92 (−7.420, 3.514)	0.401
	GG vs AG + AA	Begg's Test		0.462
		Egger's test	0.15 (−2.919, 3.207)	0.890
	GG vs AA	Begg's Test		1.000
		Egger's test	−0.25 (−4.409, 3.771)	0.820
rs7975232	C vs A	Begg's Test		0.806
		Egger's test	0.18 (−21.348, 23.925)	0.868
	CC + AC vs AA	Begg's Test		0.806
		Egger's test	−0.60 (−9.974, 6.800)	0.590
	CC vs AC + AA	Begg's Test		1.000
		Egger's test	0.21 (−10.489, 11.973)	0.847
	CC vs AA	Begg's Test		0.806
		Egger's test	0.15 (−95.868, 105.04)	0.894
rs1544410	T vs C	Begg's Test		0.707
		Egger's test	−1.01 (−6.402, 2.979)	0.368
	TT + CT vs CC	Begg's Test		0.452
		Egger's test	−1.61 (−8.677, 2.300)	0.182
	TT vs CT + CC	Begg's Test		0.707
		Egger's test	2.16 (−0.183, 1.464)	0.097
	TT vs CC	Begg's Test		0.707
		Egger's test	1.91 (−0.339, 1.840)	0.128

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