Egyptian Journal of Medical Human Genetics

META-ANALYSIS Open Access

Vitamin D receptor (VDR) gene *Fok*I, *Bsm*I, *Apa*I, and *Taq*I polymorphisms and osteoporosis risk: a meta-analysis

Upendra Yadav, Pradeep Kumar and Vandana Rai*

Abstract

Background: Osteoporosis is a disease of the bones in which the density of the bones decreases. The prevalence of this disease greatly varies in different populations of the world. Numerous studies have been investigated VDR gene polymorphisms as osteoporosis risk in different ethnic groups. In present meta-analysis, the aim is to find out the role of VDR gene polymorphisms (*Fok*I, *Bsm*I, *Apa*I, and *Taq*I) in osteoporosis risk.

Methods: Suitable case-control studies for present meta-analysis were retrieved from four electronic databases. Open Meta-Analyst program was used for statistical analyses.

Results: Studies investigated *Bsm*I (65 studies; 6880 cases/8049 controls), *Apa*I (31 studies; 3763 cases/3934 controls), *Fok*I (18 studies; 1895 cases/1722 controls), and *Taq*I (26 studies; 2458 cases/2895 controls) polymorphisms that were included in the present meta-analysis. A significant association was found between the dominant model of *Fok*I ($OR_{ff + Ffvs.FF}$ = 1.19, 95% CI = 1.04–1.36, p = 0.01, I^2 = 39.36%) in the overall analysis and recessive model of the Caucasian population of *Taq*I polymorphism ($OR_{TT + Ttvs.tt}$ = 1.35, 95% CI = 1.11–1.63, p = 0.002, I^2 = 50.07%) with osteoporosis. On the other hand, no such effect is found in any other genetic models and in any other gene polymorphisms of the overall analyses or sub-group analyses.

Conclusion: In conclusion, the authors found that the dominant model of *Fok*I in the overall analysis and recessive model of *Taq*I in the Caucasian population are significantly associated with the development of osteoporosis.

Keywords: Osteoporosis; Vitamin D receptor, *Bsm*I, *Apa*I, *Fok*I, *Taq*I

Background

Bone is an active tissue that maintains itself by continuous formation and reabsorption [1]. Osteoporosis is a condition in which the density of the bone decreases due to the increased activity of the osteoclasts [2]. A great variance is observed in the prevalence of osteoporosis in different ethnic groups [3]. Age and gender are the two major contributing factors in the occurrence of osteoporosis. Worldwide, one out of three women over the age of 50 experiences osteoporotic fractures in comparison to one in five men of the same age group [4]. Genetic and environmental factors play a crucial role in the etiology of osteoporosis [5, 6]. Calcium intake and exercise are the main risk factors for osteoporosis [5]. It is very well established that along with the environmental factors, individual genetics plays a key role in the development of osteoporosis, e.g., (i) low bone density is found in the female offspring of the osteoporotic women [7], (ii) male offspring of idiopathic osteoporotic men have low bone mineral density [8], and (iii) studies of female twins have shown heritability of bone mineral density (BMD) to be 57 to 92% [9, 10].

Amongst all the genes studied in osteoporosis, the vitamin D receptor (VDR) gene polymorphism is the most important in the etiology of the disease [11, 12]. *VDR* gene polymorphisms have been reported to be

* Correspondence: raivandana@rediffmail.com
Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, (UP), Jaunpur 222 003, India

associated with the development of several bone diseases, multiple sclerosis, vitamin D-dependent rickets type II, and other complex diseases [13]. However, the mechanism by which the *VDR* gene influences bone mass has not been fully elucidated.

In human, VDR gene is found on the chromosome 12 (12q12-q14) with 11 exons and spans ~ 75 kb genomic DNA. The most studied VDR gene polymorphisms are *Bsm*I, *Apa*I, *Fok*I, and *Taq*I. Although several studies between osteoporosis and VDR gene polymorphisms have been published, the results are contradictory [14, 15]. This may be due to the differences in the designing of the studies, less number of samples, differences in ethnicities, or various other environmental factors. So, the aim of the present study was to find an association between VDR gene polymorphisms and osteoporosis risk.

Methods

Different databases (PubMed, Google Scholar, SpringerLink, and Science direct) were searched up to December 31, 2018, with the keywords "vitamin D receptor gene," "*Bsm*I," "*Apa*I," "*Fok*I," "*Taq*I," and "VDR," along with "osteoporosis." The retrieved studies were conducted between 1995 and 2018, and we examined all the retrieved papers thoroughly to determine their suitability for inclusion in the current meta-analysis.

Inclusion and exclusion criteria

Studies found suitable to be included in the present study should have (a) a case-control study and (b) reported the sample size and distribution of genotypes. Similarly, a study should be excluded if (a) the study was conducted on the animal model, (b) the study that has

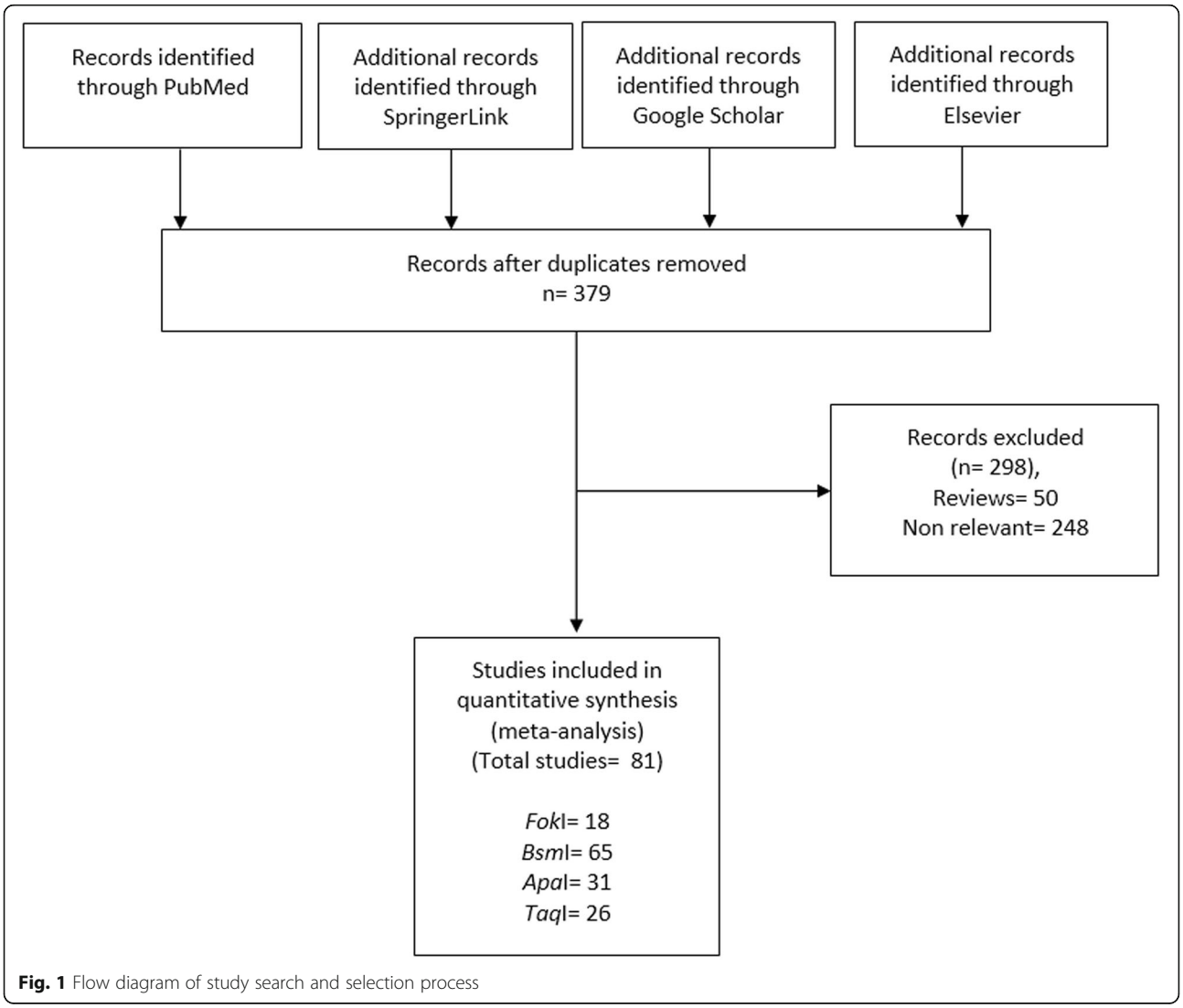

Fig. 1 Flow diagram of study search and selection process

replication of data, (c) only cases were reported, and (d) book chapters or review articles.

Data extraction

From the selected articles, we extracted different information like (a) last name of the first author, (b) year of publication of the study, (c) country where the study was conducted, and (d) number of genotypes in different groups. We also checked whether the genotype distributions of control population of all the included studies were in agreement with Hardy–Weinberg equilibrium (HWE) by using the goodness of fit chi-squared test. All the data from the different papers were retrieved by the two authors (UY and PK) and if any discrimination was found, it was resolved by the consultation with the corresponding author.

Statistical analysis

Meta-analysis was done according to the method given in Rai et al. [16]. Briefly, statistical analysis of different vitamin D receptor gene polymorphisms and risk of osteoporosis were estimated by pooling the odds ratio (OR) with its corresponding 95% confidence intervals (CI). Heterogeneity was tested using Q statistics (a p value of less than 0.05 was considered significant). The I^2 statistics was also used to assess the discrepancy between studies. If the heterogeneity was higher (p value of Q test < 0.05 or I^2 > 50%) than the random effect model [17] that was applied, fixed effect model [18] was used. The heterogeneity may arise due to the differences in ethnicities or variation in study design or outcome. The funnel plot of precision by log odds ratio and standard error by log odds ratio was assessed for the possible publication bias, and if the funnel plot was found asymmetric, it denoted a publication bias [19]. The linear regression method of Egger was used to measure the asymmetry in the funnel plot [20], and a statistically significant publishing bias was considered to be a p value of < 0.05. The meta-analysis was conducted by Open Meta-Analyst program [21].

Results

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was followed in the present meta-analysis. Flow chart of article selection was shown in Fig. 1 with specific reasons. Eighty-one studies were found to be eligible for

Table 1 Summary estimates for the odds ratio (OR) of *Bsm*I in various allele/genotype contrasts, the significance level (p value) of heterogeneity test (Q test), and the I^2 metric

Gene	Genetic contrast	Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity p value (Q test)	I^2 (%)	Publication bias (p of Egger's test)
Overall (65)	Allele contrast (b vs. B)	0.90 (0.85–0.94), < 0.001	0.89 (0.78–1.01), 0.09	< 0.001	82.02	0.73
	Dominant (bb + Bb vs. BB)	0.84 (0.77–0.92), < 0.001	0.81 (0.68–0.97), 0.02	< 0.001	65.61	0.34
	Homozygote (bb vs. BB)	0.81 (0.73–0.90), < 0.001	0.77 (0.60–0.99), 0.04	< 0.001	76.01	0.58
	Co-dominant (Bb vs. BB)	0.88 (0.80–0.97), 0.01	0.85 (0.73–0.98), 0.03	< 0.001	43.51	0.33
	Recessive (BB + Bb vs. bb)	0.89 (0.83–0.96), 0.004	0.88 (0.74–1.06), 0.20	< 0.001	77.37	0.94
Asian (22)	Allele Contrast (b vs. B)	0.84 (0.74–0.95), 0.008	0.86 (0.61–1.19), 0.36	< 0.001	81.58	0.92
	Dominant (bb + Bb vs. BB)	0.70 (0.55–0.90), 0.005	0.70 (0.46–1.06), 0.09	0.007	47.66	0.91
	Homozygote (bb vs. BB)	0.63 (0.47–0.84), 0.002	0.64 (0.34–1.22), 0.17	< 0.001	68.37	0.70
	Co-dominant (Bb vs. BB)	0.77 (0.59–1.00), 0.05	0.75 (0.58–0.98), 0.03	0.84	0	0.79
	Recessive (BB + Bb vs. bb)	0.86 (0.72–1.03), 0.10	0.84 (0.56–1.27), 0.42	< 0.001	75.82	0.78
Caucasian (37)	Allele contrast (b vs. B)	0.87 (0.82–0.92), < 0.001	0.86 (0.74–1.00), 0.05	< 0.001	81.09	0.74
	Dominant (bb + Bb vs. BB)	0.85 (0.77–0.94), 0.003	0.84 (0.69–1.04), 0.11	< 0.001	69.26	0.57
	Homozygote (bb vs. BB)	0.78 (0.69–0.88), < 0.001	0.76 (0.57–1.02), 0.06	< 0.001	77.36	0.63
	Co-dominant (Bb vs. BB)	0.91 (0.82–1.02), 0.11	0.90 (0.75–1.08), 0.29	< 0.001	52.43	0.72
	Recessive (BB + Bb vs. bb)	0.82 (0.75–0.90), < 0.001	0.81 (0.66–1.00), 0.05	< 0.001	75.5	0.72
Other (6)	Allele contrast (b vs. B)	1.28 (1.08–1.51), 0.003	1.19 (0.76–1.85), 0.43	< 0.001	84.7	0.45
	Dominant (bb + Bb vs. BB)	1.00 (0.75–1.33), 0.96	0.82 (0.40–1.67), 0.59	< 0.001	80.11	0.31
	Homozygote (bb vs. BB)	1.50 (1.08–2.10), 0.01	1.27 (0.54–3.00), 0.57	< 0.001	80.65	0.54
	Co-dominant (Bb vs. BB)	0.77 (0.57–1.05), 0.10	0.62 (0.31–1.24), 0.18	< 0.001	75.66	0.17
	Recessive (BB + Bb vs. bb)	1.69 (1.32–2.16), < 0.001	1.71 (0.97–3.03), 0.06	< 0.001	78.25	0.79

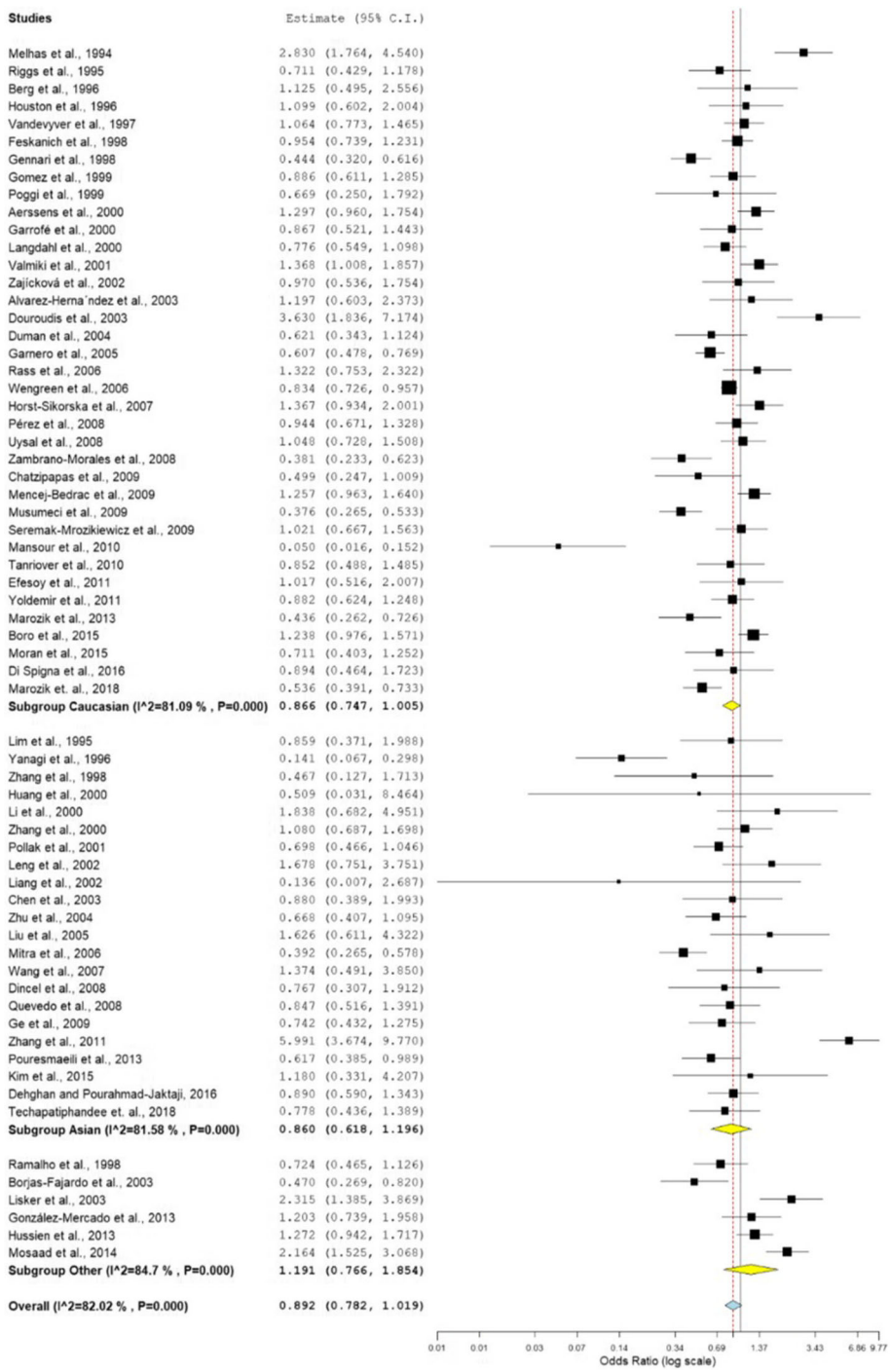

Fig. 2 Random effect forest plot of allele contrast model (b vs. B) of VDR *Bsm*I polymorphism. Results of individual and summary OR estimates, and 95% CI of each study were shown. Horizontal lines represented 95% CI, and dotted vertical lines represent the value of the summary OR

inclusion in the present meta-analysis after applying the inclusion and exclusion criteria. Out of 81 included studies, *Bsm*I, *Apa*I, *Fok*I, and *Taq*I polymorphisms were investigated in 65, 31, 18, and 26 studies respectively.

Eligible studies

For *Bsm*I, a total of 65 studies with 6880 cases and 8049 controls were included in the meta-analysis [22–86].

For *Apa*I, a total of 31 studies with 3763 cases and 3934 controls were found eligible for the meta-analysis

[24, 28, 30, 38, 44, 45, 48, 51, 56, 63, 64, 66, 69, 71, 73, 75, 77, 79, 81, 83–85, 87–95].

For *Fok*I, meta-analysis which has a total of 18 studies with 1895 cases and 1722 controls were included in the meta-analysis [38, 45, 50, 56, 61, 67, 70, 71, 73, 75, 79, 81, 84, 96–100].

For *Taq*I, a total of 26 studies including 2458 cases and 2895 controls were found eligible for inclusion in the meta-analysis [24, 28, 30, 38, 45, 48, 51, 56, 63, 64, 69, 71, 73, 75, 77, 79, 81, 83–86, 92, 93, 95, 101, 102].

Meta-analysis

BsmI meta-analysis

In allele contrast model, high heterogeneity was observed with insignificant association ($OR_{bvs.B}$ = 0.89, 95% CI = 0.78–1.01, p = 0.09, I^2 = 82.02%, $P_{heterogeneity}$ = < 0.001). No significant association was found in any other genetic models—for dominant model (bb + Bb vs. BB) OR = 0.81, 95% CI = 0.68–0.97, p = 0.02; for homozygote model (bb vs. BB) OR = 0.77, 95% CI = 0.60–0.99, p = 0.04; for co-dominant model (Bb vs. BB) OR = 0.85, 95% CI = 0.73–0.98, p = 0.03; and for recessive model (BB + Bb vs. bb) OR = 0.88, 95% CI = 0.74–1.06, p = 0.20. Heterogeneity was high in all the genetic models except in the co-dominant model (Table 1; Fig. 2).

Ethnicity was used for the sub-group analysis. Out of 65 studies, 37 belong to Caucasians, 22 were Asian, and 6 were of other origins. High heterogeneity was observed in all genetic models in all sub-groups. No significant association was found in any sub-group analyses in any genetic models (Table 1; Fig. 2).

ApaI meta-analysis

Insignificant association with high heterogeneity was found in the allele contrast model ($OR_{avs.A}$ = 1.01, 95% CI = 0.87–1.17, p = 0.86, I^2 = 74.82%, $P_{heterogeneity}$ = < 0.001). No significant association was found in any other genetic models—for dominant model (aa+Aa vs. AA) OR = 0.95, 95% CI = 0.78–1.14, p = 0.60; for homozygote model (aa vs. AA) OR = 0.97, 95% CI = 0.72–1.30, p = 0.84; for co-dominant model (Aa vs. AA) OR = 0.92, 95% CI = 0.81–1.04, p = 0.21; and for recessive model (AA+Aa vs. aa) OR = 1.02, 95% CI = 0.81–1.28, p = 0.83 (Table 2; Fig. 3).

The ethnicity-based sub-group analyses were conducted. Out of 31 studies, 15 were Caucasians, 12 were Asians, and 4 were of other origin. High heterogeneity

Table 2 Summary estimates for the odds ratio (OR) of *Apa*I in various allele/genotype contrasts, the significance level (p value) of heterogeneity test (Q test), and the I^2 metric

Gene	Genetic contrast	Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity p value (Q test)	I^2 (%)	Publication bias (p of Egger's test)
Overall (31)	Allele contrast (a vs. A)	0.99 (0.92–1.06), 0.90	1.01 (0.87–1.17), 0.86	< 0.001	74.82	0.79
	Dominant (aa+Aa vs. AA)	0.92 (0.82–1.04), 0.20	0.95 (0.78–1.14), 0.60	< 0.001	55.28	0.17
	Homozygote (aa vs. AA)	0.96 (0.83–1.11), 0.60	0.97 (0.72–1.30), 0.84	< 0.001	68.58	0.65
	Co-dominant (Aa vs. AA)	0.92 (0.81–1.04), 0.21	0.93 (0.79–1.09), 0.40	0.051	31.3	0.09
	Recessive (AA+Aa vs. aa)	1.06 (0.94–1.18), 0.30	1.02 (0.81–1.28), 0.83	< 0.001	68.95	0.50
Asian (12)	Allele contrast (a vs. A)	0.99 (0.89–1.12), 0.99	1.10 (0.84–1.45), 0.46	< 0.001	78.48	0.32
	Dominant (aa+Aa vs. AA)	1.01 (0.82–1.24), 0.90	1.09 (0.81–1.49), 0.54	0.05	43.75	0.04
	Homozygote (aa vs. AA)	0.90 (0.71–1.15), 0.43	1.03 (0.64–1.65), 0.89	0.004	60.16	0.32
	Co-dominant (Aa vs. AA)	1.14 (0.91–1.44), 0.24	1.12 (0.89–1.41), 0.32	0.83	0	0.007
	Recessive (AA+Aa vs. aa)	0.99 (0.83–1.17), 0.90	1.01 (0.70–1.46), 0.93	< 0.001	72.92	0.82
Caucasian (15)	Allele contrast (a vs. A)	0.96 (0.86–1.06), 0.45	0.92 (0.72–1.18), 0.54	< 0.001	78.00	0.49
	Dominant (aa+Aa vs. AA)	0.91 (0.77–1.08), 0.31	0.90 (0.66–1.23), 0.52	< 0.001	67.83	0.81
	Homozygote (aa vs. AA)	0.94 (0.76–1.17), 0.62	0.86 (0.52–1.42), 0.57	< 0.001	75.96	0.57
	Co-dominant (Aa vs. AA)	0.91 (0.77–1.09), 0.34	0.91 (0.70–1.19), 0.52	0.014	49.93	0.96
	Recessive (AA+Aa vs. aa)	0.98 (0.81–1.18), 0.87	0.88 (0.61–1.28), 0.53	< 0.001	68.33	0.42
Other (4)	Allele contrast (a vs. A)	1.07 (0.91–1.26), 0.38	1.07 (0.90–1.27), 0.39	0.36	5.32	0.76
	Dominant (aa+Aa vs. AA)	0.82 (0.63–1.07), 0.15	0.82 (0.62–1.07), 0.15	0.43	0	0.48
	Homozygote (aa vs. AA)	1.11 (0.79–1.55), 0.52	1.17 (0.64–1.13), 0.60	0.03	65.55	0.44
	Co-dominant (Aa vs. AA)	0.67 (0.50–0.89), 0.007	0.67 (0.50–0.89), 0.007	0.63	0	0.68
	Recessive (AA+Aa vs. aa)	1.42 (1.10–1.83), 0.007	1.49 (1.00–2.23), 0.04	0.09	52.4	0.38

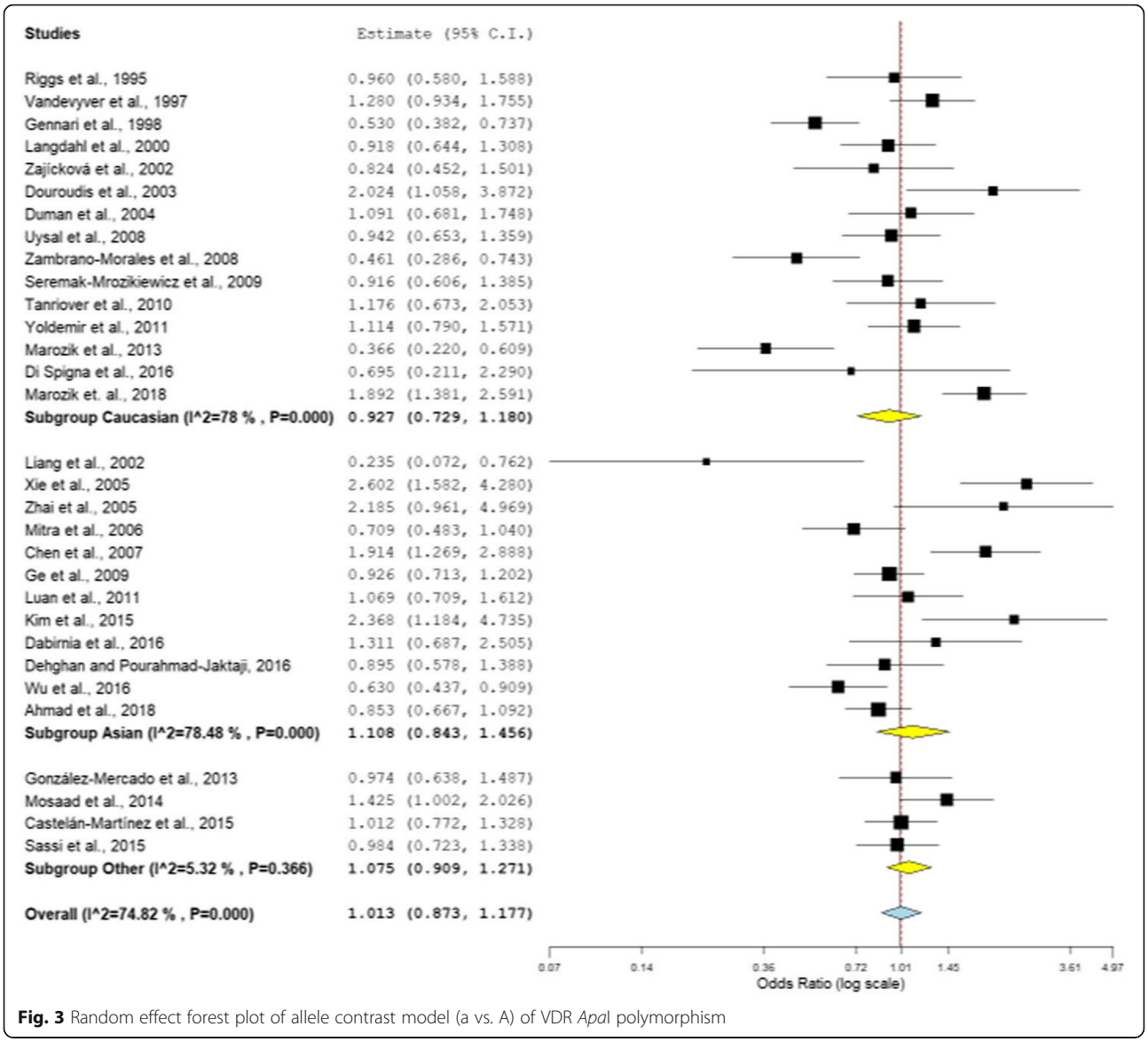

Fig. 3 Random effect forest plot of allele contrast model (a vs. A) of VDR *ApaI* polymorphism

was observed in Caucasian studies while low heterogeneity was found in Asian and other studies. Insignificant association was found in all sub-group analyses and in all the genetic models except for the recessive model of the other studies (AA+Aa vs. aa) OR = 1.49, 95% CI = 1.00–2.23, p = 0.04 (Table 2; Fig. 3).

FokI meta-analysis

In the dominant model of *Fok*I polymorphism, significant association was found ($OR_{ff + Ffvs.FF}$ = 1.19, 95% CI = 1.04–1.36, p = 0.01, I^2 = 39.36%). No significant association was observed in any other genetic models—allele contrast model $OR_{fvs.F}$ = 1.13, 95% CI 0.95–1.34, p = 0.15, I^2 = 61.8%, $P_{heterogeneity}$ = < 0.001; homozygote model (ff vs. FF) OR = 1.38, 95% CI = 0.92–2.05, p = 0.11; co-dominant model (Ff vs. FF) OR = 1.12, 95% CI = 0.97–1.30, p = 0.11; and recessive model (FF + Ff vs. ff) OR = 1.34, 95% CI = 0.94–1.91, p = 0.10) (Table 3; Fig. 4).

Studies were further analyzed by sub-group analysis on the basis of ethnicity. Out of 18, ten studies belong to Caucasians, five were Asians, and three were of other ethnicity. High heterogeneity was found in Asian and other studies; while in the Caucasian studies, low heterogeneity was observed. No significant association was found in any sub-group in any genetic model (Table 3; Fig. 4).

TaqI meta-analysis

High heterogeneity with insignificant association was found in the allele contrast model of *Taq*I polymorphism

Table 3 Summary estimates for the odds ratio (OR) of *Fok*I in various allele/genotype contrasts, the significance level (*p* value) of heterogeneity test (*Q* test), and the I^2 metric

Gene	Genetic contrast	Fixed effect OR (95% CI), *p*	Random effect OR (95% CI), *p*	Heterogeneity *p* value (*Q* test)	I^2 (%)	Publication bias (*p* of Egger's test)
Overall (18)	Allele contrast (f vs. F)	1.19 (1.08–1.31), < 0.001	1.13 (0.95–1.34), 0.15	< 0.001	61.8	0.64
	Dominant (ff + Ff vs. FF)	1.19 (1.04–1.36), 0.01	1.13 (0.94–1.37), 0.18	0.04	39.36	0.40
	Homozygote (ff vs. FF)	1.47 (1.19–1.83), < 0.001	1.38 (0.92–2.05), 0.11	< 0.001	62.08	0.99
	Co-dominant (Ff vs. FF)	1.12 (0.97–1.30), 0.11	1.10 (0.93–1.29), 0.24	0.29	13.69	0.15
	Recessive (FF + Ff vs. ff)	1.40 (1.15–1.72), < 0.001	1.34 (0.94–1.91), 0.10	0.001	57.98	0.69
Asian (5)	Allele contrast (f vs. F)	1.28 (1.07–1.53), 0.007	1.17 (0.76–1.82), 0.45	< 0.001	79.79	0.50
	Dominant (ff + Ff vs. FF)	1.24 (0.96–1.59), 0.08	1.16 (0.71–1.89), 0.53	0.02	65.88	0.61
	Homozygote (ff vs. FF)	1.73 (1.18–2.52), 0.004	1.68 (0.68–4.14), 0.25	< 0.001	78.92	0.88
	Co-dominant (Ff vs. FF)	1.15 (0.87–1.52), 0.30	1.09 (0.70–1.70), 0.69	0.12	45.24	0.36
	Recessive (FF + Ff vs. ff)	1.66 (1.16–2.37), 0.005	1.60 (0.76–3.37), 0.21	0.004	73.74	0.88
Caucasian (10)	Allele contrast (f vs. F)	1.31 (0.99–1.29), 0.06	1.05 (0.86–1.29), 0.61	0.04	48.84	0.78
	Dominant (ff + Ff vs. FF)	1.15 (0.96–1.38), 0.12	1.07 (0.83–1.39), 0.57	0.09	39.58	0.65
	Homozygote (ff vs. FF)	1.27 (0.95–1.70), 0.10	1.11 (0.73–1.70), 0.61	0.09	39.35	0.28
	Co-dominant (Ff vs. FF)	1.11 (0.91–1.34), 0.27	1.07 (0.85–1.35), 0.54	0.22	23.34	0.63
	Recessive (FF + Ff vs. ff)	1.21 (0.92–1.59), 0.15	1.12 (0.78–1.61), 0.53	0.17	29.92	0.44
Other (3)	Allele contrast (f vs. F)	1.26 (0.97–1.64), 0.08	1.31 (0.84–2.04), 0.21	0.07	60.97	0.58
	Dominant (ff + Ff vs. FF)	1.24 (0.86–1.77), 0.23	1.24 (0.86–1.77), 0.23	0.62	0	0.82
	Homozygote (ff vs. FF)	1.91 (1.00–3.65), 0.05	3.28 (0.51–20.87), 0.20	0.01	78.17	0.07
	Co-dominant (Ff vs. FF)	1.11 (0.76–1.61), 0.56	1.11 (0.76–1.61), 0.56	0.74	0	0.07
	Recessive (FF + Ff vs. ff)	1.72 (0.96–3.05), 0.06	3.30 (0.49–22.00), 0.21	0.005	81.08	0.001

($OR_{tvs.T}$ = 1.10, 95% CI = 0.91–1.32, p = 0.30, I^2 = 77.26%, $P_{heterogeneity}$ = < 0.001). Insignificant association was found in the other four genetic models—dominant model (tt + Tt vs. TT) OR = 1.09, 95% CI = 0.84–1.41, p = 0.48; for homozygote model (tt vs. TT) OR = 1.20, 95% CI = 0.85–1.69, p = 0.29; for co-dominant model (Tt vs. TT) OR = 1.04, 95% CI = 0.82–1.33, p = 0.70; and for recessive model (TT + Tt vs. tt) OR = 1.16, 95% CI = 0.91–1.48, p = 0.20 (Table 4; Fig. 5).

The studies were further analyzed on the basis of ethnicity for sub-group analysis. Out of 26 studies, 17 belong to Caucasians, six were Asians, and three were of other ethnicity. High heterogeneity was observed in all groups, i.e., Asian, Caucasian, and other studies. Insignificant results were found in all the sub-groups of all the genetic models except for the recessive model of the Caucasian population (TT + Tt vs. tt) OR = 1.35, 95% CI = 1.11–1.63, p = 0.002 (Table 4; Fig. 5).

Sensitivity analysis

To conduct sensitivity analysis, all the studies deviated from the Hardy–Weinberg equilibrium (p < 0.05) were omitted. In *Bsm*I, 21 studies [27, 30, 34, 38, 39, 44, 48–52, 58, 60, 62, 64, 66, 68, 70, 71, 76, 80] were deviated from the HWE. Meta-analysis, after removal of these 21 studies, showed no significant association with osteoporosis risk in the main analysis ($OR_{bvs.B}$ = 0.99, 95% CI = 0.85–1.15, p = 0.92, I^2 = 77.48%) or in any sub-groups (Asian subgroup $OR_{bvs.B}$ = 0.99, 95% CI = 0.66–1.50, p = 0.99, I^2 = 83.65%; Caucasian subgroup $OR_{bvs.B}$ = 0.96, 95% CI = 0.83–1.11, p = 0.65, I^2 = 69.61%; and other studies subgroup $OR_{bvs.B}$ = 1.24, 95% CI = 0.64–2.43, p = 0.51, I^2 = 86.53%). When these 21 studies were removed, heterogeneity was decreased in both the overall and in the sub-group meta-analyses except in the Asian studies.

In total of 18 *Fok*I studies, control population in five studies [56, 70, 79, 99, 100] was not in HWE. When these studies were removed from the analysis, insignificant association was found in the main analysis ($OR_{fvs.F}$ = 1.12, 95% CI = 0.99–1.26, p = 0.05, I^2 = 46.48%), and no association was found in any sub-group. Removal of these studies decreases the heterogeneity both in the overall and in sub-group meta-analyses.

The control samples of nine *Apa*I studies [28, 30, 44, 48, 51, 56, 71, 83, 94] were not in HWE. Result of meta-analysis after removal of these nine studies showed no association between *Apa*I polymorphism and osteoporosis risk in the main/overall analysis ($OR_{avs.A}$ = 1.07, 95% CI = 0.90–1.27, p = 0.39, I^2 = 73.94%) and

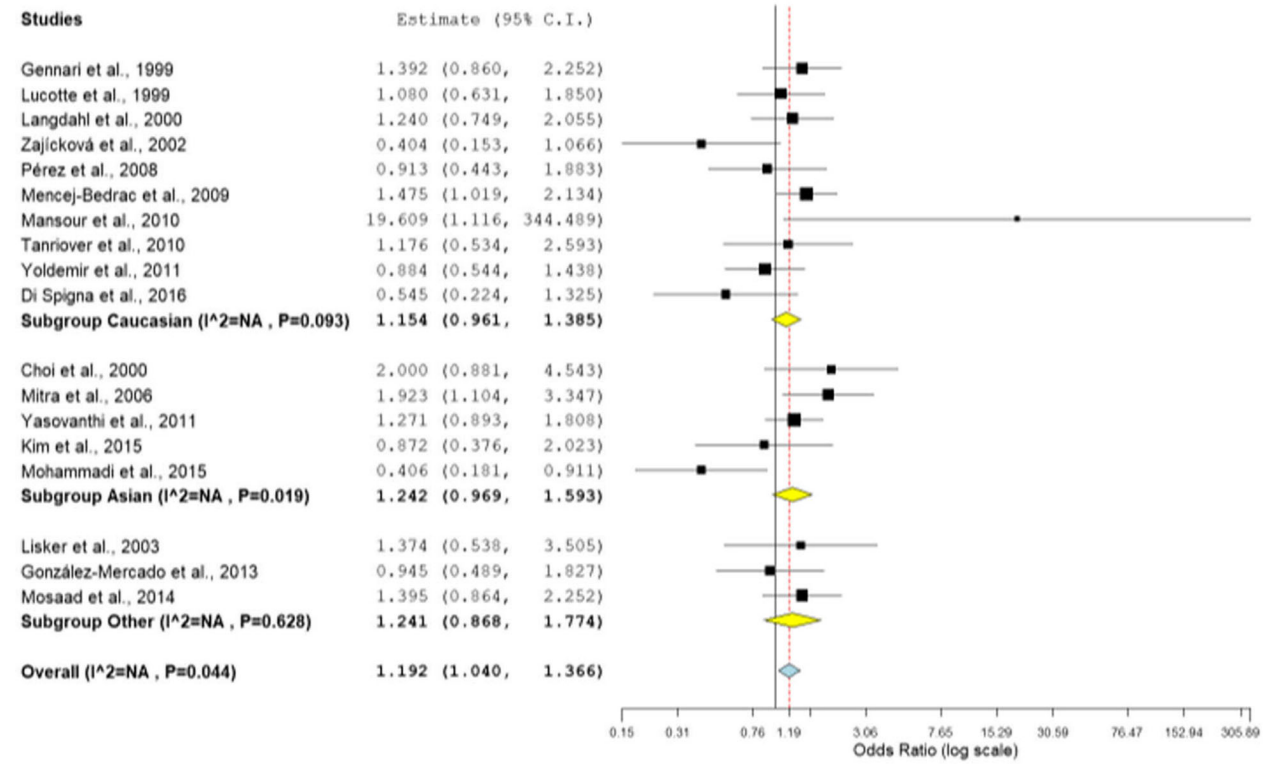

Fig. 4 Fixed effect forest plot of dominant model (ff + Ff vs. FF) of VDR *Fok*I polymorphism

Caucasian population ($OR_{avs.A}$ = 0.85, 95% CI = 0.63–1.16, p = 0.32, I^2 = 78.62%) but the Asian population ($OR_{avs.A}$ = 1.42, 95% CI = 1.03–*1.96*, p = 0.03, I^2 = 77.61%) and subgroup other studies (recessive model $OR_{AA + Aavs.aa}$ = 1.49, 95% CI = 1.00–2.23, p = 0.04, I^2 = 52.4%) showed statistically significant association with osteoporosis. Heterogeneity was also decreased both in the overall and sub-group meta-analyses.

Out of 26 *Taq*I studies, control samples of the four studies [28, 56, 77, 101] were deviated from the HWE. Results of meta-analysis of 22 studies (after elimination of 4 studies deviated from HWE) did not show any association between *Taq*I polymorphism and osteoporosis risk either in total studies (OR_{tvsT} = 1.05, 95% CI = 0.85–1.29, p = 0.63, I^2 = 78.86%) or in any sub-group. Moreover, after removal of these 4 studies, there was an increase in the heterogeneities in overall and sub-group meta-analyses except the Asian population.

Publication bias

In all the genetic models in the overall and in sub-group meta-analyses for all polymorphisms, the funnel plots were symmetrical (Fig. 6; Tables 1–4) except recessive model of the other studies in *Fok*I and co-dominant model of the Asian studies in *Apa*I polymorphisms. Similarly, no publication bias was found in any genetic model in overall meta-analyses of all the four polymorphisms by the Egger's test except recessive model of the other studies in *Fok*I and co-dominant model of the Asian studies in *Apa*I polymorphism (Tables 1–4).

Discussion

The vitamin D receptors are the members of the nuclear hormone receptor (NR1I) family and expressed in different organs like the intestine, thyroid, and kidney in humans [103]. It is primarily responsible for the endocrine action of vitamin D that regulates calcium homeostasis and reduces the risk of osteoporosis. VDR is translocated from the cytoplasm to the nucleus when activated by binding of its ligand 1α,25-dihydroxyvitamin D_3 (1, $25(OH)_2D_3$) [104]. Several studies have documented that the onset of osteoporosis is caused by VDR gene polymorphisms [81]. VDR gene polymorphisms are also associated with other diseases like breast cancer [105], diabetes [106], myocardial infarction [107], and metabolic syndrome and inflammation [108].

Meta-analysis is a well-established statistical tool used for combining the data of small sample-sized individual studies. Meta-analysis increases the power of the study and decreases type I and II errors. During the past two decades, a number

Table 4 Summary estimates for the odds ratio (OR) of *Taq*I in various allele/genotype contrasts, the significance level (*p* value) of heterogeneity test (*Q* test), and the I^2 metric

Gene	Genetic Contrast	Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity *p* value (*Q* test)	I^2 (%)	Publication bias (*p* of Egger's test)
Overall (26)	Allele contrast (t vs. T)	1.08 (0.99–1.17), 0.06	1.10 (0.91–1.32), 0.30	< 0.001	77.26	0.67
	Dominant (tt + Tt vs. TT)	1.05 (0.93–1.18), 0.38	1.09 (0.84–1.41), 0.48	< 0.001	75.22	0.47
	Homozygote (tt vs. TT)	1.18 (0.99–1.39), 0.05	1.20 (0.85–1.69), 0.29	< 0.001	70.17	0.76
	Co-dominant (Tt vs. TT)	1.01 (0.89–1.15), 0.84	1.04 (0.82–1.33), 0.70	< 0.001	68.06	0.51
	Recessive (TT + Tt vs. tt)	1.19 (1.02–1.38), 0.02	1.16 (0.91–1.48), 0.20	< 0.001	52.95	0.87
Asian (6)	Allele contrast (t vs. T)	0.94 (0.79–1.12), 0.49	0.99 (0.67–1.47), 0.99	0.003	72.15	0.65
	Dominant (tt + Tt vs. TT)	0.84 (0.66–1.07), 0.17	0.92 (0.54–1.56), 0.76	0.005	70.38	0.61
	Homozygote (tt vs. TT)	1.00 (0.69–1.43), 0.99	1.08 (0.52–2.23), 0.82	0.03	58.57	0.70
	Co-dominant (Tt vs. TT)	0.80 (0.61–1.03), 0.09	0.86 (0.52–1.41), 0.55	0.025	61.12	0.66
	Recessive (TT + Tt vs. tt)	1.09 (0.79–1.52), 0.58	1.11 (0.72–1.72), 0.62	0.23	26.09	0.73
Caucasian (17)	Allele contrast (t vs. T)	1.24 (1.11–1.38), < 0.001	1.22 (0.99–1.50), 0.05	< 0.001	71.32	0.69
	Dominant (tt + Tt vs. TT)	1.31 (1.12–1.53), < 0.001	1.28 (0.95–1.74), 0.09	< 0.001	69.87	0.69
	Homozygote (tt vs. TT)	1.46 (1.18–1.82), < 0.001	1.40 (0.94–2.09), 0.09	< 0.001	66.06	0.67
	Co-dominant (Tt vs. TT)	1.24 (1.05–1.47), 0.009	1.22 (0.91–1.64), 0.16	< 0.001	63.75	0.67
	Recessive (TT + Tt vs. tt)	1.35 (1.11–1.63), 0.002	1.28 (0.96–1.71), 0.08	0.01	50.07	0.48
Other (3)	Allele contrast (t vs. T)	0.76 (0.62–0.94), 0.01	0.74 (0.39–1.39), 0.35	< 0.001	88.27	0.81
	Dominant (tt + Tt vs. TT)	0.69 (0.52–0.92), 0.01	0.65 (0.31–1.36), 0.44	< 0.001	71.34	0.65
	Homozygote (tt vs. TT)	0.66 (0.43–1.00), 0.05	0.63 (0.17–2.26), 0.48	< 0.001	86.46	0.84
	Co-dominant (Tt vs. TT)	0.70 (0.52–0.95), 0.02	0.67 (0.38–1.19), 0.17	0.034	70.35	0.62
	Recessive (TT + Tt vs. tt)	0.77 (0.52–1.15), 0.05	0.76 (0.29–1.99), 0.58	0.009	78.57	0.89

of meta-analyses were published which assessed the polymorphism of small effect genes as risk factor for different diseases and disorders, e.g., Down syndrome [16], neural tube defects [109], Glucose 6-phosphate dehydrogenase deficiency [110], depression [111], schizophrenia [112], Alzheimer [113], breast cancer [114], colorectal cancer [115], esophageal cancer [116], and prostate cancer [117].

During literature search, we identified seven meta-analyses [15, 118–123] investigating the relationship between VDR gene polymorphisms and osteoporosis. *Bsm*I, *Apa*I, *Fok*I, and *Taq*I polymorphisms were included in seven, four, two, and two meta-analyses respectively. *Bsm*I polymorphism studies were included in all seven meta-analyses. In six meta-analyses, no significant association was found between osteoporosis susceptibility and *Bsm*I polymorphism [15, 118–122]. Zhang et al [123] conducted a meta-analysis of the risk of osteoporosis in postmenopausal women with 36 studies including 7192 subjects and found a marginally significant association ($OR_{bvs.B}$ = 1.2; CI = 1.00–1.46; *p* =

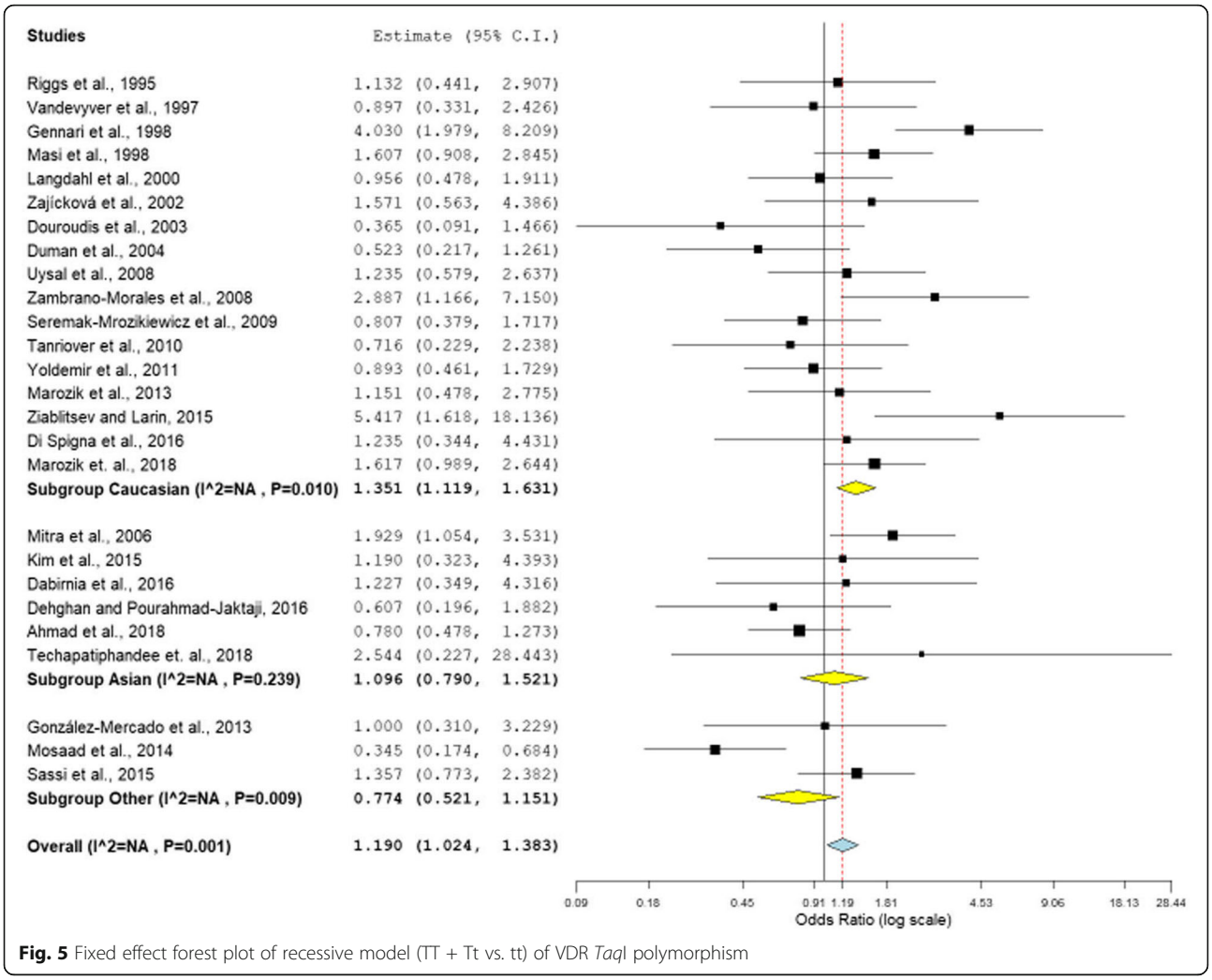

Fig. 5 Fixed effect forest plot of recessive model (TT + Tt vs. tt) of VDR *Taq*I polymorphism

0.052). In all the meta-analyses, a low between study heterogeneity was found in all the studies except the study conducted by Yu et al [120]. *Apa*I polymorphism was included in four meta-analyses [118, 120, 122, 123]. Zintzaras et al [118], Yu et al [120], Wang et al [122], and Zhang et al [123] included seven, six, three, and eighteen studies, respectively, in their meta-analyses, and all four studies reported no association between *Apa*I polymorphism and osteoporosis risk. Zintzaras et al [118] and Zhang et al [123] conducted meta-analyses of three and 18 studies of *Fok*I polymorphism, and no significant association was found between *Fok*I polymorphism and osteoporosis. Both groups [118, 123] also conducted meta-analyses of *Taq*I polymorphism studies and again reported no association between *Taq*I polymorphism and osteoporosis susceptibility.

In the present meta-analysis, four common VDR gene polymorphisms (*Bsm*I, *Apa*I, *Fok*I, and *Taq*I) were included. A total of 65 (14929 samples), 31 (7697 samples), 18 (3617 samples), and 26 (5353 samples) studies for *Bsm*I, *Apa*I, *Fok*I, and *Taq*I polymorphisms, respectively, were included. We found a significant association in the dominant model of *Fok*I polymorphism (ff + Ff vs. FF OR = 1.19, 95% CI = 1.04–1.36, p = 0.01) with low heterogeneity (I^2 = 39.36). No association was found in sub-group analysis on the basis of ethnicity in any genetic model except in the Caucasian population in the recessive model of *Taq*I polymorphism (TT + Tt vs. tt OR = 1.35, 95% CI = 1.11–1.63, p = 0.002) with moderate heterogeneity (I^2 = 50.07). The frequency of different VDR gene polymorphisms varies in different ethnic/regional populations. Due to this, the effect of these polymorphisms might vary from population to population.

The present meta-analysis has few demerits like (i) used crude odds ratio, (ii) only genetic polymorphisms considered, and other factors such as environmental factors or food habits that are not included which might have important roles in the etiology of osteoporosis.

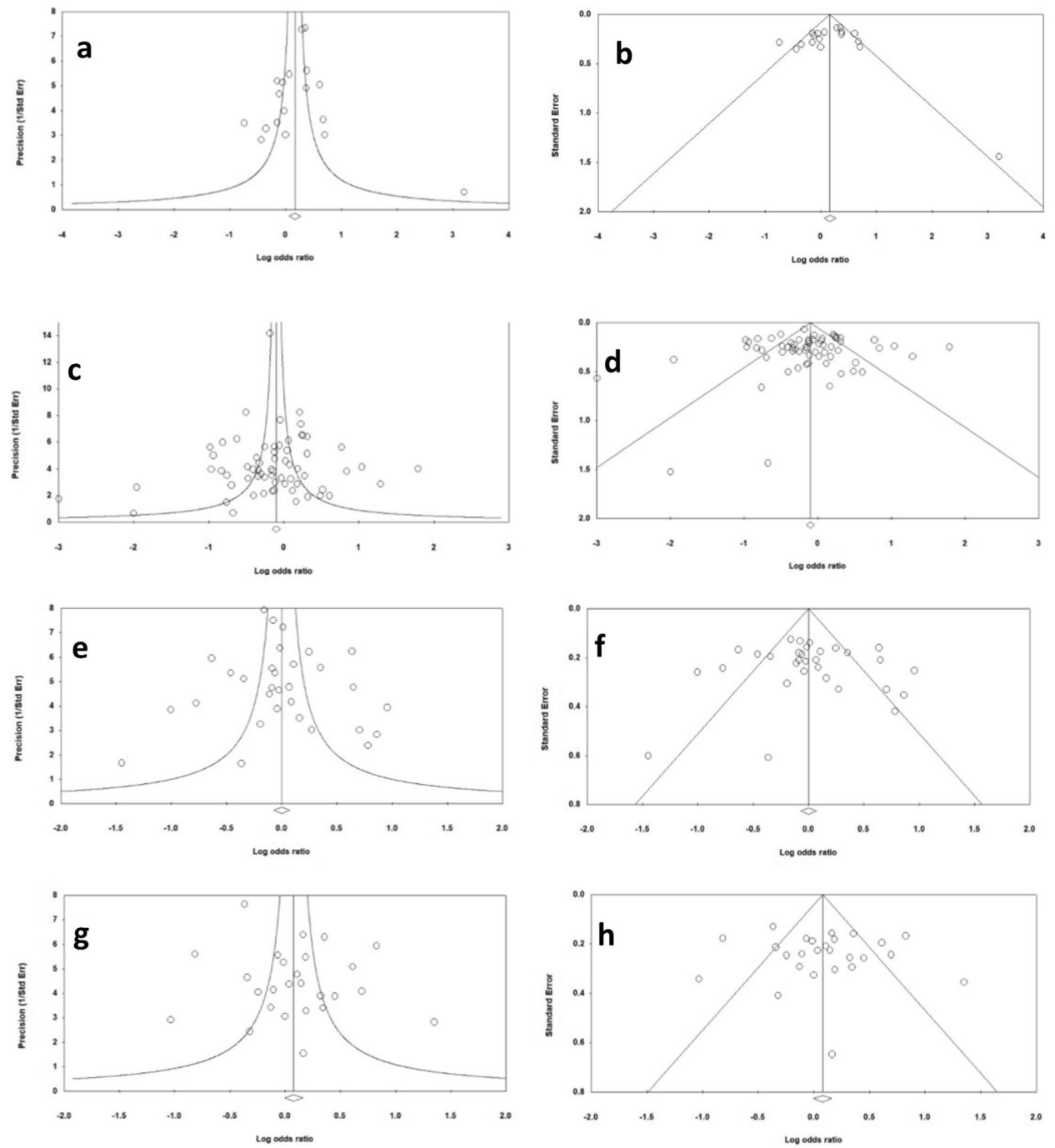

Fig. 6 Funnel plots for *Fok*I. **a** Precision by log odds ratio. **b** Standard error by log odds ratio for *Bsm*I. **c** Precision by log odds ratio. **d** Standard error by log odds ratio for *Apa*I. **e** Precision by log odds ratio. **f** Standard error by log odds ratio for *Taq*I. **g** Precision by log odds ratio. **h** Standard error by log odds ratio

With these limitations, the present study has some strength like (i) this is the largest meta-analysis conducted both in number of included studies and number of sample size (81 studies; 19268 samples) and (ii) included all common VDR polymorphisms (*Bsm*I, *Apa*I, *Fok*I, and *Taq*I).

Conclusion

In conclusion, we found that the dominant model of *Fok*I polymorphism is associated with osteoporosis, and also the recessive model of *Taq*I polymorphism is a risk factor for the osteoporosis in the Caucasian population. The other polymorphisms (*Bsm*I and *Apa*I) have no role

in the osteoporosis in total or in the stratified populations. In addition, it has been suggested that different gene-gene and gene-environment interactions should also be considered in future case-control studies, which could clarify the genetics of osteoporosis.

Abbreviations

BMD: Bone mineral density; VDR: Vitamin D receptor gene; HWE: Hardy–Weinberg equilibrium; OR: Odds ratio; 95%CI: 95% confidence intervals; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; FE: Fixed effect; RE: Random effect; I^2: Inconsistency between studies; Q: Cochran's test

Acknowledgements

Upendra Yadav is highly grateful to the VBS Purvanchal University, Jaunpur, for providing financial assistance to him in the form of PDF.

Authors' contributions

UP and PK have retrived articles , both have extracted data from the included studies, and VR and UY written the manuscript. All author(s) have read and approved the manuscript.

Funding

There was no funding for this review.

Availability of data and materials

The data and materials will be available with the corresponding author upon reasonable request.

Ethics approval and consent to participate

The article does not contain any studies with human or animal subjects performed by any of the authors.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 4 November 2019 Accepted: 9 March 2020
Published online: 13 April 2020

References

1. Manolagas SC (2000) Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev. 21(2):115–137
2. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC (1998) Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids, Potential mechanisms of their deleterious effects on bone. J Clin Investig. 102:274
3. Faucki A, Eugene B, Dennis L, Stephen L, Dan L, Jameson J. Harrison's Principles of internal medicine. Vol II. 17th ed. McGrow-Hill; 2008.
4. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A et al (2000) Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int. 11(8):669–674
5. Nieves JW (1999) Osteoporosis: the role of micronutrients. Am J Clin Nutr. 81:1232S–1239S
6. Recker RR (2004) Genetic research in osteoporosis: where are we? Where should we go next? J Musculoskelet Neuronal Interact. 4:86–90
7. van Leeuwen JP, Uitterlinden AG, Birkenhäger JC, Pols HA (1996) Vitamin D receptor gene polymorphisms and osteoporosis. Steroids. 61:154–156
8. Van Pottelbergh I, Goemaere S, Zmierczak H, De Bacquer D, Kaufman J (2003) Deficient acquisition of bone during maturation underlies idiopathic osteoporosis in men: evidence from a three-generation family study. J Bone Miner Res. 18:303–311
9. Harris M, Nguyen T, Howard G, Kelly P, Eisman J (1998) Genetic and environmental correlations between bone formation and bone mineral density: a twin study. Bone. 22:141–145
10. Nguyen T, Howard G, Kelly P, Eisman JA (1998) Bone mass, lean mass, and fat mass: same genes or same environments? Am J Epidemiol. 147:3–16
11. Brandi ML, Gennari L, Cerinic MM, Becherini L, Falchetti A, Masi L et al (2001) Genetic markers of osteoarticular disorders: facts and hopes. Arthritis Res. 3:270–280
12. Ioannidis JP, Stavrou I, Trikalinos TA, Zois C, Brandi ML, Gennari L et al (2002) Association of polymorphisms of the estrogen receptor gene with bone mineral density and fracture risk in women: a meta-analysis. J Bone Miner Res. 17(11):2048–2060
13. Cantorna MT, Mahon BD (2004) Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med. 229:1136–1142
14. Thakkinstian A, D'Este C, Eisman J, Nguyen T, Attia J. Meta-analysis of molecular association studies: vitamin D receptor gene polymorphisms and BMD as a case study. J Bone Miner Res. 12004;9:419-28.
15. Qin G, Dong Z, Zeng P, Liu M, Liao X (2013) Association of vitamin D receptor BsmI gene polymorphism with risk of osteoporosis: a meta-analysis of 41 studies. Mol Biol Rep. 40(1):497–506
16. Rai V, Yadav U, Kumar P, Yadav SK, Mishra OP (2014) Maternal methylenetetrahydrofolate reductase C677T polymorphism and down syndrome risk: a meta-analysis from 34 studies. PLoS One. 9:e108552
17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials. 7:177–188
18. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 22(4):719–748
19. Stuck AE, Rubenstein LZ, Wieland D (1998) Bias in meta-analysis detected by a simple, graphical test Asymmetry detected in funnel plot was probably due to true heterogeneity. BMJ. 316:469
20. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ. 315:629–634
21. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P et al (2013) Closing the gap between methodologists and endusers: R as a computational back-end. J Stat Software. 49:1–15
22. Melhus H, Kindmark A, Amer S, Wilen B, Lindh E, Ljunghall S (1994) Vitamin D receptor genotypes in osteoporosis. Lancet. 344:949–950
23. Lim SK, Park YS, Park JM, Song YD, Lee EJ, Kim KR et al (1995) Lack of association between vitamin D receptor genotypes and osteoporosis in Koreans. J Clin Endocrinol Metab. 80(12):3677–3681
24. Riggs BL, Nguyen TV, Melton LJ 3rd, Morrison NA, O'Fallon WM, Kelly PJ et al (1995) The contribution of vitamin D receptor gene alleles to the determination of bone mineral density in normal and osteoporotic women. J Bone Miner Res. 10(6):991–996
25. Berg JP, Falch JA, Haug E (1996) Fracture rate, pre- and postmenopausal bone mass and early and late postmenopausal bone loss are not associated with vitamin D receptor genotype in a high-endemic area of osteoporosis. Eur J Endocrinol. 135:96–100
26. Houston LA, Grant SF, Reid DM, Ralston SH (1996) Vitamin D receptor polymorphism, bone mineral density, and osteoporotic vertebral fracture: studies in a UK population. Bone. 18:249–252
27. Yanagi H, Tomura S, Kawanami K, Hosokawa M, Tanaka M, Kobayashi K et al (1996) Vitamin D receptor gene polymorphisms are associated with osteoporosis in Japanese women. J Clin Endocrinol Metab. 81(11):4179–4181
28. Vandevyver C, Wylin T, Cassiman JJ, Raus J, Geusens P (1997) Influence of the vitamin D receptor gene alleles on bone mineral density in postmenopausal and osteoporotic women. J Bone Miner Res. 12(2):241–247
29. Feskanich D, Hunter DJ, Willett WC, Hankinson SE, Hollis BW, Hough HL et al (1998) Vitamin D receptor genotype and the risk of bone fractures in women. Epidemiology. 9:535–539
30. Gennari L, Becherini L, Masi L, Mansani R, Gonnelli S, Cepollaro C et al (1998) Vitamin D and estrogen receptor allelic variants in Italian postmenopausal women: evidence of multiple gene contribution to bone mineral density. J Clin Endocrinol Metab. 83(3):939–944
31. Ramalho AC, Lazaretti-Castro M, Hauache O, Kasamatsu T, Brandao C, Reis AF et al (1998) Fractures of the proximal femur: correlation with vitamin D receptor gene polymorphism. Braz J Med Biol Res. 31:921–927
32. Zhang H, Tao G, Wu Q (1998) Preliminary studies on the relationship between vitamin D receptor gene polymorphism and osteoporosis in Chinese women. Zhonghua Liu Xing Bing Xue Za Zhi. 19(1):12–14
33. Gómez C, Naves ML, Barrios Y, Díaz JB, Fernández JL, Salido E et al (1999) Vitamin D receptor gene polymorphisms, bone mass, bone loss and prevalence of vertebral fracture: differences in postmenopausal women and men. Osteoporos Int. 10(3):175–182

34. Poggi M, Aterini S, Nicastro L, Chiarugi V, Ruggiero M, Pacini S et al (1999) Lack of association between body weight, bone mineral density and vitamin D receptor gene polymorphism in normal and osteoporotic women. Dis Markers. 15(4):221–227
35. Aerssens J, Dequeker J, Peeters J, Breemans S, Broos P, Boonen S (2000) Polymorphisms of the VDR, ER and COLIA1 genes and osteoporotic hip fracture in elderly postmenopausal women. Osteoporos Int. 11(7):583–591
36. Fontova Garrofé R, Gutiérrez Fornés C, Broch Montané M, Aguilar Crespillo C, Pujol del Pozo A, Vendrell Ortega J et al (2000) Polymorphism of the gene for vitamin D receptor, bone mass, and bone turnover in women with postmenopausal osteoporosis. Rev Clin Esp. 200(4):198–202
37. Huang X, Zhu W, Liu Y, An X, Chen X (2000) Analysis of the correlation between vitamin D receptor gene polymorphisms and bone mineral density. Chin J Orthop. 20:372–374
38. Langdahl BL, Gravholt CH, Brixen K, Eriksen EF (2000) Polymorphisms in the vitamin D receptor gene and bone mass, bone turnover and osteoporotic fractures. Eur J Clin Invest. 30(7):608–617
39. Li Y, Yang Y, Li D, Cai X, Li Z, Xu L (2000) Vitamin D receptor gene polymorphisms and bone mineral density in postmenopausal women. J Tianjin Med Univ. 6:263–264
40. Zhang Q, Wang W, Kuang J, Shen H, Huang H, Jiang N (2000) Relationship between the polymorphism of vitamin D receptor gene and bone mineral density in pre- and postmenopausal women. Acad J Sun Yat-Sen Univ Med Sci. 21:376–379
41. Pollak RD, Blumenfeld A, Bejarano-Achache I, Idelson M, Celinke HD (2001) The BsmI vitamin D receptor gene polymorphism in Israeli populations and in perimenopausal and osteoporotic Ashkenazi women. Am J Nephrol. 21(3):185–188
42. Valimaki S, Tahtela R, Kainulainen K, Laitinen K, Loyttyniemi E, Sulkava R et al (2001) Relation of collagen type I alpha 1 (COLIA 1) and vitamin D receptor genotypes to bone mass, turnover, and fractures in early postmenopausal women and to hip fractures in elderly people. Eur J Intern Med. 12:48–56
43. Leng XW, Chen RY, Liya A, Hong L, Yinhua J, Guoshu T et al (2002) The relationship between vitamin D receptor gene and bone mineral density in osteoporosis in Urumchi area. Chin J Endocrinol Metab. 18:123
44. Liang W, Xiu L, Liang Y, Yu B (2002) The association between Vitamin D receptor gene polymorphism and osteoporosis. Acad J Sun Yat-Sen Univ Med Sci. 23:47–49
45. Zajickova K, Zofkova I, Bahbouh R, Krepelova A (2002) Vitamin D receptor gene polymorphisms, bone mineral density and bone turnover: FokI genotype is related to postmenopausal bone mass. Physiol Res. 51(5):501–509
46. Alvarez-Hernández D, Naves M, Díaz-López JB, Gómez C, Santamaría I, Cannata-Andía JB (2003) Influence of polymorphisms in VDR and COLIA1 genes on the risk of osteoporotic fractures in aged men. Kidney Int Suppl. 85:S14–S18
47. Chen J, Li YH, Zhang LP, Qiu TF, Peng H, Deng ZL et al (2003) The relationship between vitamin D receptor gene and bone mineral density in osteoporosis in Chongqing area. Chongqing Med J. 32:881–882
48. Douroudis K, Tarassi K, Ioannidis G, Giannakopoulos F, Moutsatsou P, Thalassinos N et al (2003) Association of vitamin D receptor gene polymorphisms with bone mineral density in postmenopausal women of Hellenic origin. Maturitas. 45(3):191–197
49. Borjas-Fajardo L, Zambrano M, Fernandez E, Pineda L, Machin A, de Romero P et al (2003) Analysis of Bsm I polymorphism of the vitamin D receptor (VDR) gene in Venezuelan female patients living in the state of Zulia with osteoporosis. Investigacion Clinica. 44:275–282
50. Lisker R, López MA, Jasqui S (2003) Ponce De León Rosales S, Correa-Rotter R, Sánchez S, et al. Association of vitamin D receptor polymorphisms with osteoporosis in mexican postmenopausal women. Hum Biol. 75(3):399–403
51. Duman BS, Tanakol R, Erensoy N, Ozturk M, Yilmazer S (2004) Vitamin D receptor alleles, bone mineral density and turnover in postmenopausal osteoporotic and healthy women. Med Princ Pract. 13(5):260–266
52. Zhu M, Yan X, Wang F, Chen Y, Huang Z (2004) The relationship between VDR gene polymorphism and BMD in postmenopausal women in Zhuang and Han populations in Guangxi Area. Chin J Osteoporos. 10:140–142
53. Garnero P, Munoz F, Borel O, Sornay-Rendu E, Delmas PD (2005) Vitamin D receptor gene polymorphisms are associated with the risk of fractures in postmenopausal women, independently of bone mineral density. J Clin Endocrinol Metab. 90(8):4829–4835
54. Horst-Sikorska W, Wawrzyniak A, Celczyńska-Bajew L, Marcinkowska M, Dabrowski S, Kalak R et al (2005) Polymorphism of VDR gene – the most effective molecular marker of osteoporotic bone fractures risk within postmenopausal women from Wielkopolska region of Poland. Endokrynol Pol. 56(3):233–239
55. Liu J, Mao Y, He P, Gou S, Zhang Y, Chen L et al (2005) Study on the relationship between vitamin D receptor gene polymorphisms and bone mineral density in old men. Chin J Osteoporos. 11:159–163
56. Mitra S, Desai M, Ikram KM (2006) Vitamin D receptor gene polymorphisms and bone mineral density in postmenopausal Indian women. Maturitas. 55(1):27–35
57. Rass P, Pákozdi A, Lakatos P, Zilahi E, Sipka S, Szegedi G et al (2006) Vitamin D receptor gene polymorphism in rheumatoid arthritis and associated osteoporosis. Rheumatol Int. 26(11):964–971
58. Wengreen H, Cutler DR, Munger R, Willing M (2006) Vitamin D receptor genotype and risk of osteoporotic hip fracture in elderly women of Utah: an effect modified by parity. Osteoporos Int. 17:1146–1153
59. Wang X, Zhu X, Nie Y, Li X (2007) Analysis of relationship between vitamin D receptor gene polymorphism and osteoporotic fracture. Chin J Osteoporos. 13:692–695
60. Dincel E, Sepici-Dincel A, Sepici V, Ozsoy H, Sepici B (2008) Hip fracture risk and different gene polymorphisms in the Turkish population. Clinics (Sao Paulo). 63:645–650
61. Pérez A, Ulla M, García B, Lavezzo M, Elías E, Binci M et al (2008) Genotypes and clinical aspects associated with bone mineral density in Argentine postmenopausal women. J Bone Miner Metab. 26(4):358–365
62. Quevedo LI, Martinez BM, Castillo NM, Rivera FN (2008) Vitamin D receptor gene polymorphisms and risk of hip fracture in Chilean elderly women. Rev Med Chil. 136:475–481
63. Uysal AR, Sahin M, Gursoy A, Gullu S (2008) Vitamin D receptor gene polymorphism and osteoporosis in the Turkish population. Genet Test. 12(4):591–594
64. Zambrano-Morales M, Borjas L, Fernández E, Zabala W, de Romero P, Pineda L et al (2008) Association of the vitamin D receptor gene BBAAtt haplotype with osteoporosis in post-menopausic women. Invest Clin. 49(1):29–38
65. Chatzipapas C, Boikos S, Drosos GI, Kazakos K, Tripsianis G, Serbis A (2009) Polymorphisms of the vitamin D receptor gene and stress fractures. Horm Metab Res. 41(8):635–640
66. Ge JR, Xie LH, Chen K, Zeng XA, Lai YL, Li SQ et al (2009) Association of genetic polymorphisms in several vitamin D receptor gene sites with bone mineral density and biochemical markers of bone turnover in postmenopausal women. J Clin Rehabil Tissue Eng Res. 13(28):5593–5596
67. Mencej-Bedrac S, Prezelj J, Kocjan T, Teskac K, Ostanek B, Smelcer M et al (2009) The combinations of polymorphisms in vitamin D receptor, osteoprotegerin and tumour necrosis factor superfamily member 11 genes are associated with bone mineral density. J Mol Endocrinol. 42(3):239–247
68. Musumeci M, Vadalà G, Tringali G, Insirello E, Roccazzello AM, Simpore J et al (2009) Genetic and environmental factors in human osteoporosis from Sub-Saharan to Mediterranean areas. J Bone Miner Metab. 27(4):424–434
69. Seremak-Mrozikiewicz A, Drews K, Mrozikiewicz PM, Bartkowiak-Wieczorek J, Marcinkowska M, Wawrzyniak A et al (2009) Correlation of vitamin D receptor gene (VDR) polymorphism with osteoporotic changes in Polish postmenopausal women. Neuro Endocrinol Lett. 30(4):540–546
70. Mansoura L, Sedky M, AbdelKhader M, Sabry R, Kamal M, El-Sawah H (2010) The role of vitamin D receptor genes (FOKI and BSMI) polymorphism in osteoporosis. Middle East Fertil Soc J. 15(2):79–83
71. Tanriover MD, Tatar GB, Uluturk TD, Erden DD, Tanriover A, Kilicarslan A et al (2010) Evaluation of the effects of vitamin D receptor and estrogen receptor 1 gene polymorphisms on bone mineral density in postmenopausal women. Clin Rheumatol. 29(11):1285–1293
72. Efesoy A, Yilmaz O, Erden G, Güçtekin A, Bodur H, Yildirimkaya M (2011) Relationship of the vitamin D receptor and collagen I(alpha)1 gene polymorphisms with low bone mineral density and vertebral fractures in postmenopausal Turkish women. Turk J Rheumatol. 26(4):295–303
73. Yoldemir T, Yavuz DG, Anik G, Verimli N, Erenus M (2011) Vitamin D receptor gene polymorphisms in a group of postmenopausal Turkish women: association with bone mineral density. Climacteric. 14(3):384–391
74. Zhang H, Su PJ, Chen F (2011) Relationship between vitamin D receptor gene polymorphism and bone mineral density and traditional Chinese medicine differentiation type in postmenopausal women in Zhongshan area of Guangdong. Chin J Tradit Med Traumatol Orthop. 2:19–21
75. González-Mercado A, Sánchez-López JY, Regla-Nava JA, Gámez-Nava JI, González-López L, Duran-Gonzalez J et al (2013) Association

analysis of vitamin D receptor gene polymorphisms and bone mineral density in postmenopausal Mexican-Mestizo women. Genet Mol Res. 12(3):2755–2763
76. Hussien YM, Shehata A, Karam RA, Alzahrani SS, Magdy H, El- Shafey AM. Polymorphism in vitamin D receptor and osteoprotegerin genes in Egyptian rheumatoid arthritis patients with and without osteoporosis. Mol Biol Rep. 2013;40:3675-3680.
77. Marozik P, Mosse I, Alekna V, Rudenko E, Tamulaitienė M, Ramanau H et al (2013) Association between polymorphisms of VDR, COL1A1, and LCT genes and bone mineral density in Belarusian women with severe postmenopausal osteoporosis. Medicina (Kaunas, Lithuania) 49(4):177–184
78. Pouresmaeili F, Jamshidi J, Azargashb E, Samangouee S (2013) Association between Vitamin D Receptor Gene BsmI polymorphism and bone mineral density in a population of 146 Iranian women. Cell J. 15(1):75–82
79. Mosaad YM, Hammad EM, Fawzy Z, Abdal Aal IA, Youssef HM, ElSaid TO et al (2014) Vitamin D receptor gene polymorphism as possible risk factor in rheumatoid arthritis and rheumatoid related osteoporosis. Hum Immunol. 75(5):452–461
80. Boroń D, Kamiński A, Kotrych D, Bogacz A, Uzar I, Mrozikiewicz PM et al (2015) Polymorphism of vitamin D3 receptor and its relation to mineral bone density in perimenopausal women. Osteoporos Int. 26:1045–1052
81. Kim SW, Lee JM, Ha JH, Kang HH, Rhee CK, Kim JW et al (2015) Association between vitamin D receptor polymorphisms and osteoporosis in patients with COPD. Int J Chron Obstruct Pulmon Dis. 10:1809–1817
82. Moran JM, Pedrera-Canal M, Rodriguez-Velasco FJ, Vera V, Lavado-Garcia JM, Fernandez P et al (2015) Lack of association of vitamin D receptor BsmI gene polymorphism with bone mineral density in Spanish postmenopausal women. PeerJ. 3:e953
83. Dehghan M, Pourahmad-Jaktaji R (2016) The effect of some polymorphisms in vitamin D receptor gene in menopausal women with osteoporosis. J Clin Diagn Res. 10(6):RC06–RC10
84. Di Spigna G, Del Puente A, Covelli B, Abete E, Varriale E, Salzano S et al (2016) Vitamin D receptor polymorphisms as tool for early screening of severe bone loss in women patients with rheumatoid arthritis. Eur Rev Med Pharmacol Sci. 20(22):4664–4669
85. Marozik PM, Tamulaitiene M, Rudenka E, Alekna V, Mosse I, Rudenka A et al (2018) Association of vitamin D receptor gene variation with osteoporosis risk in Belarusian and Lithuanian postmenopausal women. Front Endocrinol (Lausanne) 9:305
86. Techapatiphandee M, Tammachote N, Tammachote R, Wongkularb A, Yanatatsaneejit P (2018) VDR and TNFSF11 polymorphisms are associated with osteoporosis in Thai patients. Biomed Rep. 9(4):350–356
87. Xie YM, Hu SN, Han H, Kou QA, Gao R, Du BJ (2005) The relationship between VDR I, VDR II-1, VDR II-2 and bone mineral density in osteoporosis in Beijing. Wuhan and Fujian. Chin J Osteoporos. 11:54–57
88. Zhai M, Liang L, Yang R (2005) Association of vitamin D receptor gene polymorphism with osteoporosis in patients with diabetes mellitus. Zhong Guo Lin Chuang Kang Fu. 9:177–179
89. Chen Z, Chen X, Wang D, Chen Y, Zhang H, Zhou Z (2007) The study of the association between Apa I polymorphism of vitamin D receptor gene and osteoporosis. Chin J Osteoporos. 13(6):402–405
90. Luan J, Fan X, Chen Z (2011) The associations between VDR gene polymorphisms and osteoporosis. Zhong guo zu zhi gong cheng yan jiu. 15:9486–9490
91. Castelan-Martinez OD, Vivanco-Munoz N, Falcon-Ramirez E, Valdes-Flores M, Clark P (2015) Apa1 VDR polymorphism and osteoporosis risk in postmenopausal Mexican women. Gaceta medica de Mexico. 151:472–476
92. Sassi R, Sahli H, Souissi C, Sellami S, Ben Ammar El Gaaied A (2015) Polymorphisms in VDR gene in Tunisian postmenopausal women are associated with osteopenia phenotype. Climacteric. 18(4):624–630
93. Dabirnia R, Mahmazi S, Taromchi A, Nikzad M, Saburi E (2016) The relationship between vitamin D receptor (VDR) polymorphism and the occurrence of osteoporosis in menopausal Iranian women. Clin Cases Miner Bone Metab. 13(3):190–194
94. Wu J, Shang DP, Yang S, Fu DP, Ling HY, Hou SS et al (2016) Association between the vitamin D receptor gene polymorphism and osteoporosis. Biomed Rep. 5(2):233–236
95. Ahmad I, Jafar T, Mahdi F, Arshad M, Das SK, Waliullah S et al (2018) Association of vitamin D receptor (FokI and BsmI) gene polymorphism with bone mineral density and their effect on 25-hydroxyvitamin D level in North Indian postmenopausal women with osteoporosis. Indian J Clin Biochem. 33(4):429–437
96. Gennari L, Becherini L, Mansani R, Masi L, Falchetti A, Morelli A et al (1999) FokI polymorphism at translation initiation site of the vitamin D receptor gene predicts bone mineral density and vertebral fractures in postmenopausal Italian women. J Bone Mine Res. 14(8):1379–1386
97. Lucotte G, Mercier G, Burckel A (1999) The vitamin D receptor FokI start codon polymorphism and bone mineral density in osteoporotic postmenopausal French women. Clinical genetics. 56:221–224
98. Choi YM, Jun JK, Choe J, Hwang D, Park SH, Ku SY et al (2000) Association of the vitamin D receptor start codon polymorphism (FokI) with bone mineral density in postmenopausal Korean women. J Hum Genet. 45(5):280–283
99. Yasovanthi J, Venkata Karunakar K, Sri Manjari K, Pulla Reddy B, Ajeya Kumar P, Sesha Charyulu M et al (2011) Association of vitamin D receptor gene polymorphisms with BMD and their effect on 1, 25-dihydroxy vitamin D3 levels in pre- and postmenopausal South Indian women from Andhra Pradesh. Clin Chim Acta. 412(7-8):541–544
100. Mohammadi Z, Keshtkar A, Fayyazbakhsh F, Ebrahimi M, Amoli MM, Ghorbani M et al (2015) Prevalence of osteoporosis and vitamin D receptor gene polymorphisms (FokI) in an Iranian general population based study (Kurdistan) (IMOS). Med J Islam Repub Iran. 29:238
101. Masi L, Becherini L, Colli E, Gennari L, Mansani R, Falchetti A et al (1998) Polymorphisms of the calcitonin receptor gene are associated with bone mineral density in postmenopausal Italian women. Biochem Biophys Res Commun. 248(1):190–195
102. Ziablitsev DS, Larin OS (2015) Influence of single nucleotide polymorphisms of vitamin D receptor-gene on the level of osteoassociated hormones linkage with postmenopausal osteoporosis. Fiziol Zh. 61(5):21–27
103. Nejentsev S, Godfrey L, Snook H, Rance H, Nutland S, Walker NM et al (2004) Comparative high resolution analysis of linkage disequilibrium and tag single nucleotide polymorphisms between populations in the vitamin D receptor gene. Hum Mol Genet. 13:1633–1639
104. Carlberg C, Dunlop TW (2006) An integrated biological approach to nuclear receptor signaling in physiological control and disease. Crit Rev Eukaryot Gene Expr. 16(1):1–22
105. McKay JD, McCullough ML, Ziegler RG, Kraft P, Saltzman BS et al (2009) Vitamin D receptor polymorphisms and breast cancer risk: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer Epidemiol Biomarkers Prev. 18(1):297–305
106. Angel B, Lera L, Márquez C, Albala C (2018) The association of VDR polymorphisms and type 2 diabetes in older people living in community in Santiago de Chile. Nutr Diabetes. 8(1):31
107. Dorsch MP, Nemerovski CW, Ellingrod VL, Cowger JA, Dyke DB, Koelling TM et al (2014) Vitamin D receptor genetics on extracellular matrix biomarkers and hemodynamics in systolic heart failure. J Cardiovasc Pharmacol Ther. 19(5):439–445
108. Zaki M, Kamal S, Basha WA, Youness E, Ezzat W, El-Bassyouni H et al (2017) Association of vitamin D receptor gene polymorphism (VDR) with vitamin D deficiency, metabolic and inflammatory markers in Egyptian obese women. Genes Dis. 4(3):176–182
109. Yadav U, Kumar P, Yadav SK, Mishra OP, Rai V (2015) Polymorphisms in folate metabolism genes as maternal risk factor for neural tube defects: an updated meta-analysis. Metab Brain Dis. 30:7–14
110. Kumar P, Yadav U, Rai V (2016) Prevalence of glucose-6-phosphate dehydrogenase deficiency in India: an updated meta-analysis. Egypt J Med Hum Genet. 17:295–302
111. Rai V (2014) Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) gene and susceptibility to depression in Asian population: a systematic meta-analysis. Cell Mol Biol 60(3):29–36
112. Rai V, Yadav U, Kumar P, Yadav SK, Gupta S (2017) Methylenetetrahydrofolate reductase A1298C genetic variant & risk of schizophrenia: a meta-analysis. Indian J Med Res. 145(4):437–447
113. Rai V (2016) Folate pathway gene methylenetetrahydrofolate reductase C677T polymorphism and Alzheimer disease risk in Asian population. Indian J Clin Biochem. 31(3):245–252
114. Rai V (2014) Methylenetetrahydrofolate reductase A1298C polymorphism and breast cancer risk: a meta-analysis of 33 studies. Ann Med Health Sci Res. 4(6):841–851
115. Rai V (2016) Evaluation of the MTHFR C677T polymorphism as a risk factor for colorectal cancer in Asian populations. Asian Pac J Cancer Prev. 16(18): 8093–8100

116. Kumar P, Rai V (2018) MTHFR C677T polymorphism and risk of esophageal cancer: an updated meta-analysis. Egypt J Med Hum Genet. 19:273–284
117. Yadav U, Kumar P, Rai V (2016) Role of MTHFR A1298C gene polymorphism in the etiology of prostate cancer: a systematic review and updated meta-analysis. Egypt J Med Hum Genet. 17(2):141–148
118. Zintzaras E, Rodopoulou P, Koukoulis GN (2006) BsmI, TaqI, ApaI and FokI polymorphisms in the vitamin D receptor (VDR) gene and the risk of osteoporosis: a meta-analysis. Dis Markers. 22(5-6):317–326
119. Jia F, Sun RF, Li QH, Wang DX, Zhao F, Li JM et al (2013) Vitamin D receptor BsmI polymorphism and osteoporosis risk: a meta-analysis from 26 studies. Genet Test Mol Biomarkers. 17(1):30–34
120. Yu M, Chen GQ, Yu F (2016) Lack of association between vitamin D receptor polymorphisms ApaI (rs7975232) and BsmI (rs1544410) and osteoporosis among the Han Chinese population: a meta-analysis. Kaohsiung J Med Sci. 32(12):599–606
121. Zhao B, Zhang W, Du S, Zhou Z (2016) Vitamin D receptor BsmI polymorphism and osteoporosis risk in post-menopausal women. Arch Med Sci. 12(1):25–30
122. Wang QX, Zhao SM, Zhou YB, Zhang C (2018) Lack of association between vitamin D receptor genes BsmI as well as ApaI polymorphisms and osteoporosis risk: a pooled analysis on Chinese individuals. Int J Rheum Dis. 21(5):967–974
123. Zhang L, Yin X, Wang J, Xu D, Wang Y, Yang J et al (2018) Associations between VDR gene polymorphisms and osteoporosis risk and bone mineral density in postmenopausal women: a systematic review and meta-analysis. Sci Rep. 8(1):981

Publisher's Note