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The Association between Vitamin D Receptor FokI Gene Polymorphism and Osteoporosis in Postmenopausal Women: A Meta-Analysis

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Abstract

Objective: The aim of this study was to quantitatively summarize the evidence for VDR FokI gene polymorphism and osteoporosis risk in postmenopausal women.

Materials and methods: Electronic search at PubMed, EMBASE, Weipu database, and Wanfang database was conducted to select studies. Case-control studies containing available genotype frequencies of F/f were chosen, and Odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of this revelance.

Results: The case-control studies including 2199 osteoporosis cases and 2231 controls were identified. Overall meta-analysis indicated that individuals with the homozygous ff genotype had increased risk of osteoporosis(Recessive model: OR=1.551, 95% CI: 1.035~2.325,p=0.034).In the stratified analysis, individuals with the ff genotype in the Recessive model had increased risk of osteoporosis in Asian subjects(OR=2.644, 95% CI: 1.583~4.419,p= 0.000),but not in Caucasian subjects(OR= 1.288, 95%CI: 0.783~2.118, p = 0.318) and Mixed subjects (OR= 0.885, 95%CI: 0.686~1.141, p =0.346). A symmetric funnel plot, the Begg- test (P=0.094) suggested that lack of publication bias. The studies conducted in each of the defined number of osteoporosis—had no effect of the FokI polymorphism on osteoporosis except for the ff versus Ff+FF genotype comparison for osteoporosis subgroup.

Conclusion: In conclusion, our meta-analysis suggests that VDR Fok I genotype is associated with increased risk of osteoporosis in Asian but not in caucasian. To draw comprehensive and true conclusions, further prospective studies with larger numbers of participants worldwide are needed to examine associations between VDR Fok I polymorphism and osteoporosis.

Keywords: Vitamin D receptor; Fok I polymorphism; Osteoporosis; Postmenopausal; Meta-analysis

Introduction

Osteoporosis is a progressive **bone disease** that is characterised by a decrease in bone mass and density and that leads to an increased risk of **fracture**. In osteoporosis, the **bone mineral density** (BMD) is reduced, bone microarchitecture deteriorates, and the amount and variety of proteins in bone are altered. Both environmental and genetic factors are the etiology of osteoporosis. In addition, family and twin studies show that osteoporosis is a multi-gene regulation, strong hereditary diseases [1]. Osteoporosis and osteoporotic fractures had brought serious harms to families and societies due to its high incidence, mortality, and medical costs [2]. The early identification of a person who is at risk to develop osteoporotic fractures is therefore of major clinical interest. Morrison's study have shown that vitamin D receptor has been associated with Bone Mineral Density (BMD), which is the major determinant of osteoporosis risk [3,4]. Since then, many factors about the relationship between gene polymorphism, BMD and fracture were intensively investigated, such as typecollagen gene, calcitonin receptor gene, low-density lipoprotein receptor related protein gene and cannabinoid receptor genes [5-7]. However, vitamin D receptor gene is the most studied and controversial gene.

Vitamin D receptor gene is located on chromosome 12 (12q13.1), longer than 100 kb. Through the genome of a single nucleotide polymorphism frequency analysis, the vitamin D receptor gene polymorphism should be more than 100 kinds [8,9]. We know vitamin D receptor gene polymorphisms mainly related to four single nucleotide polymorphisms (BsmI, TaqI, ApaI and FokI) from recent study [10]. Fang et al. performed a meta-analysis relating BsmI or TaqI polymorphisms of the VDR gene with Osteoporosis risk [11]. They searched published studies from 1996 to September 2005 through PubMed and evaluated the genetic effect of the BsmI and TaqI polymorphism of VDR on fracture risk and found out that there was no relationship between the VDR BsmI or TaqI polymorphism and fracture risk.

Postmenopausal osteoporosis is a common disease associated with aging, mainly in postmenopausal eldly women, which seriously affect their health and quality of life, and even shorten life expectancy [12-14]. Gross et al. [15] conducted a study in postmenopausal Mexican-American women, showed that FokI polymorphism of the VDR gene correlates significantly with decreased BMD at the lumbar spine and an increased rate of bone loss at the hip in ff subjects. In

another study of postmenopausal Italian women population, Gennari L [16] observed a weak association between FokI polymorphism and lumbar BMD (p = 0.06) but no reveland to femoral neck BMD(p = 0.5). Base on VDR biological functions, FokI can be seen as a candidate gene for osteoporosis. Accumulating studies have investigated the association between this polymorphism and osteoporosis [17,18]. However, the results were inconsistent. Therefore, we conducted a meta-analysis to quantitatively assess the effect of the FokI polymorphism on the risk of osteoporosis.

Materials and Methods

Publication search

We searched the PubMed,EMBASE,Weipu database and Wanfang database for all articles on the association between VDR FokI and osteoporosis risklast search updateAugust 21, 2014. The following key words were used 'VDR FokI', 'polymorphism' and 'osteoporosis' or 'fracture'. Case-control studies containing available genotype frequencies of FokI were chosen. Of the studies with overlapping data published by the same author, only the most recent or complete study was included in this meta-analysis.

Statistic analysis

For control group of each study, the observed genotype frequencies of the VDR FokI polymorphism were assessed for Hardy Weinberg – EquilibriumHWE using the $\chi 2$ test. The strength of association between VDR FokI gene and osteoporosis was accessed by calculating crude odds ratios (ORs) and 95% confidence intervals (CIs). The pooled ORs were performed for additive genetic model (f vs.F), dominant model (ff+Ff vs. FF), and recessive model (ff vs. Ff+ FF) respectively. Heterogeneity assumption was evaluated by a chi-square based Q-test. A significant Q-statistic (P<0.05) indicated heterogeneity across studies. The summary OR estimate of each study was calculated by he fixed-effects model if there was not significant heterogeneity. Otherwise, the random-effects model was employed [19,20]. The potential for publication bias was examined by a Begg's test (funnel plot method) and Egger's linear regression test (P<0.05 considered representative of statistical significance) [21]. All analyses were performed using Stata software (version 9.0; Stata Corporation, College Station, TX).

Results

Eligible studies

We identified 12 studies on the association between VDR FokI and osteoporosis, including 2199 osteoporosis and 2231 controls in our meta-analysis (Figure 1 and Table 1).

Five studies [16, 22-25] were performed in Caucasians and another five investigations [26-30] were conducted in Asians. Furthermore, two reports [14,31] were from mixed ethnicities. The data of our interest were extracted: first author's surname, year of publication and the number of cases and controls for VDR FokI genotypes (Table 1). The distribution of genotypes in the controls of the studies were in agreement with Hardy–Weinberg equilibrium, except two study [26,28].

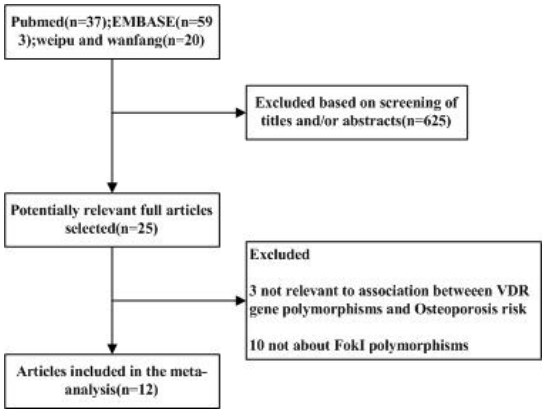

Figure 1: Flow chart indicating search results

Author	year	Ethnicity a	Osteoporosis				Control			Pb
			FF	Ff	ff		FF	Ff	ff	
Yasovanthi J [26]	2011	Asian	177	201	49		219	225	16	<0.05
Xing SJ [27]	2011	Asian	7	14	11		27	35	8	0.51
Mitra S [28]	2006	Asian	38	42	39		46	33	18	0.011
Zhang ZL [29]	2002	Asian	40	23	3		29	27	5	0.711
Choi YM [30]	2000	Asian	12	23	13		26	33	6	0.327
Ozbas H [22]	2012	Caucasian	48	23	4		63	36	8	0.377
Mencej-Bedrac S [23]	2009	Caucasian	88	108	44		105	97	26	0.618
Zajickova K [24]	2002	Caucasian	26	28	11		7	21	5	0.111
Langdahl BL [25]	2002	Caucasian	28	41	10		34	31	15	0.11
Gennari L [16]	1999	Caucasian	60	73	31		53	55	11	0.542
Wengreen H [31]	2006	Mixed	329	367	123		322	389	143	0.168
Lisker R [14]	2003	Mixed	27	29	9		20	29	8	0.625

Table 1: The distribution of VDR FokI genotypes for osteoporosis and controls; a: Ethnicity: Mixed: mixed ethnicities. b: p value for Hardy–Weinberg equilibrium in control group

Meta-analysis

Differences in allelic distribution by ethnicity could be partially responsible for the observed differences in the association between VDR FokI and osteoporosis. The results of the association between the

VDR FokI polymorphism, osteoporosis and the heterogeneity test are shown in Table 2.

Genetice model	Population	Pooled OR [95% CI] p	Heterogeneity	Publication Bias	
			p-value	p-value	
				Begg	p-value
					Egger
Additive (f vs. F)	Caucasian	1.118 [0.854~1.464]0.418	0.072	0.014	0.019
	Asian	1.491[1.063~2.091]0.021	0.013	0.624	0.867
	Mixed	0.912 [0.797~1.043]0.180	0.848	0.317	-
	overall	1.192[0.976~1.456] 0.085	0	0.125	0
Dominant (f-carriers vs.FF)	Caucasian	1.115[0.776~1.602]0.558	0.086	0.05	0.062
	Asian	1.397[0.936~2.086]0.102	0.062	0.624	0.768
	Mixed	0.891[0.737~1.078]0.235	0.662	0.317	-
	overall	1.149[0.919~1.436]0.222	0.006	0.232	0.038
Recessive (ff vs. F-carriers)	Caucasian	1.288[0.783~2.118]0.318	0.135	0.327	0.238
	Asian	2.644[1.583~4.419]0.000	0.137	0.142	0.45
	Mixed	0.885[0.686~1.141]0.346	0.834	0.317	-
	overall	1.551[1.035~2.325]0.034	0	0.125	0.094

Table 2: ORs and 95% CI for osteoporosis and the VDR FokI polymorphism under different genetic models

The association was most pronounced for carriers of the ff genotype (recessive model: OR= 1.551, 95% CI: 1.035~2.325, p= 0.034). The positive association was driven by an Asian recessive model: (OR= 2.644, 95% CI: 1.583~4.419, p= 0.000, P = 0.137 for heterogeneity, Figure 2 and 3).

No significant association was found in Caucasians (OR=1.288, 95% CI: 0.783~2.118, p= 0.318) and Mixed (OR=0.885, 95% CI: 0.686~1.141, p= 0.3346).

The geographic and race difference might affect the results of our analysis for the association of VDR FokI gene polymorphism with osteoporosis susceptibility. In order to evaluate this effect, we divided the population by ethnicity. In Caucasians, there was no a significant association between f allele or ff homozygous and osteoporosis susceptibility (p = 0.418 and p = 0.558, respectively; Table 2), and the ff genotype seemed not to play a protective role against osteoporosis risk (p = 0.318; Table 2). However, we found that there was an most pronounced association between VDR FokI gene polymorphism and osteoporosis susceptibility in Asians (f allele: p = 0.021; ff:p = 0.000; Table 2, Figure 4).

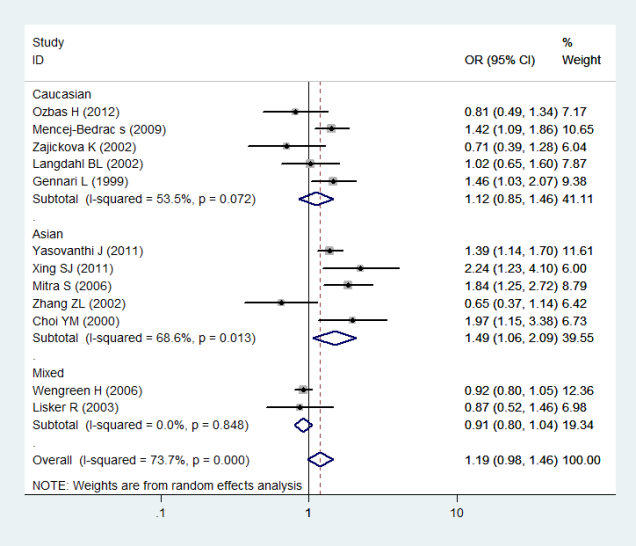

Figure 2: Additive: Forest plot of ORs of Osteoporosis FokI f allele when compared to the F allele (Additive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

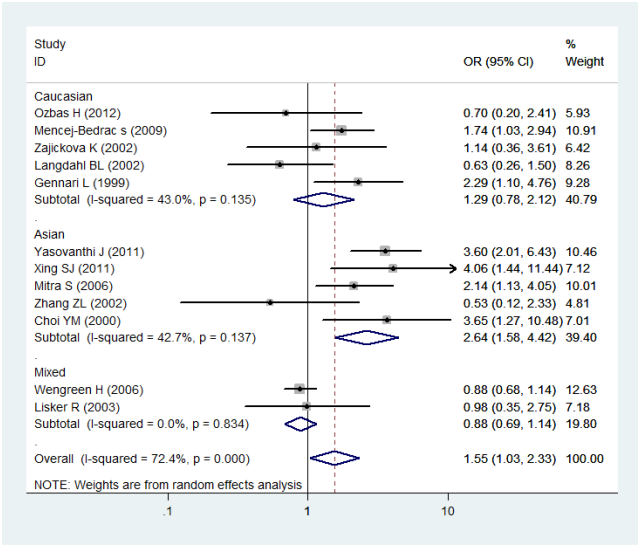

Figure 3: Recessive: Forest plot of ORs of Osteoporosis FokI ff genotype when compared to the F allele carriers (Ff +FF)(Recessive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

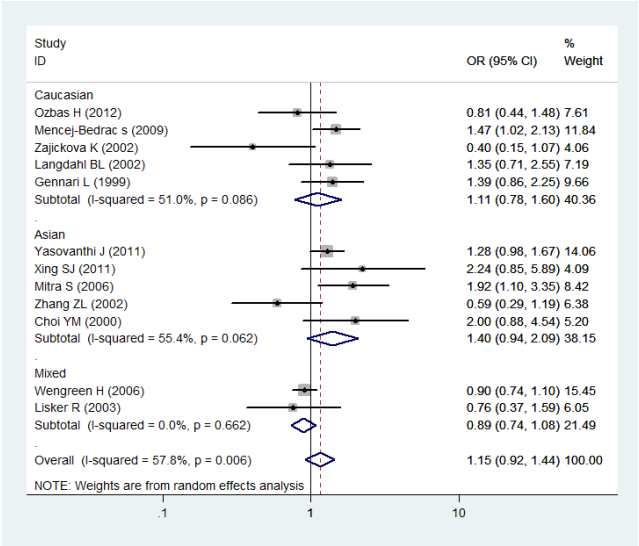

Figure 4: Dominant: Forest plot of ORs of Osteoporosis FokI f allele carriers (ff + Ff) when compared to the FF genotype(Dominant model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

Publication bias

Funnel plot and Egger's test were performed to quantitatively evaluate the publication bias of literatures on osteoporosis. The results of Begg- test provided statistical evidence for funnel plot symmetry (P=0.094) in overall results, suggesting the absence of publication bias.

Discussion

Polymorphisms of the vitamin D receptor gene (VDR) have been widely investigated with various populations. The first findings related to osteoporosis were carried out in 1994 on an Australian population of Caucasian [3]. VDR gene, has been recently postulated as a major genetic determinant of BMD and consequently of osteoporotic fracture risk [3,32,33]. Moreover, VDR FokI gene polymorphism is one of most important subtypes of VDR gene polymorphisms. This meta-analysis was performed to explore whether the VDR FokI gene polymorphism could predict the susceptibility of osteoporosis. Uitterlinden et al. [34] performed a meta-analysis including nine European research teams to explore the association of VDR Cdx2, BsmI, TaqI, ApaI and FokI polymorphisms with the risk of BMD or fracture in Caucasians, and found that the FokI, BsmI, ApaI, and TaqI VDR polymorphisms were not associated with BMD or with fractures, but the Cdx2 polymorphism might be associated with risk for vertebral fractures. Our result was different from Uitterlinden et al. [34]. In our study, we found that individuals with the homozygous ff genotype had increased risk of osteoporosis (OR=1.551, 95% CI: 1.035~2.325, p= 0.034) in overall populations. Sensitivity analysis was also performed and we found that the conclusions were similar to the nonsensitivity, and the publication bias test indicated that there was no publication bias for overall populations. The results from our study were robust. So, we might draw a conclusion that VDR Fok I gene polymorphism was associated with the susceptibility of osteoporosis.

The studies of association between Vitamin D receptor gene polymorphism and osteoporosis can provide a theoretical basis for genetic diagnosis and treatment, which might lead to early treatment and prevention of osteoporosis. In addition, genetic polymorphism can also serve as a means of predicating medication efficacy at molecular level. Understanding the relationship between medication efficacy and certain genotypes might help us to choose not only targeted treatment and prevention, but also save cost of medicines and medical. Although there were a certain correlation between vitamin D receptor genotypes with bone mineral density, the pathogenesis of osteoporosis is quite complex. Osteoporosis is a polygenic disease and regulated by multiple genes. However, environmental factors and life style also have certain influence to the expression of genes [35]. Therefore, the relationship between vitamin D receptor gene polymorphisms and osteoporosis should be multi-center and large sample studies, and considering the synergy of many factors.

In conclusion, our results support a genetic association between VDR Fokpolymorphisms and osteoporosis in overall populations but not in caucasians. Large studies might be necessary to validate this association in different populations incorporated with environmental factors in the susceptibility of osteoporosis.

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