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To cite this version:

Zahra Mohammadi, Fateme Fayyazbakhsh, Mehdi Ebrahimi, Mahsa Amoli, Patricia Khashayar, et al.. Association between vitamin D receptor gene polymorphisms (Fok1 and Bsm1) and osteoporosis: a systematic review. Journal of Diabetes Metabolic Disorders, BioMed Central, 2014, 13 (1), pp.98. 10.1186/s40200-014-0098-x. inserm-01218470

HAL Id: inserm-01218470
https://www.hal.inserm.fr/inserm-01218470
Submitted on 21 Oct 2015

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Association between vitamin D receptor gene polymorphisms (Fok1 and Bsm1) and osteoporosis: a systematic review

Zahra Mohammadi1, Fatemeh Fayyazbakhsh2,3, Mehdi Ebrahimi3, Mahsa M Amoli3,4,7*, Patricia Khashayar2,3, Mahboubeh Dini5, Reza Nezam Zadeh1, Abbasali Keshtkar2,3 and Hamid Reza Barikani6

Abstract

Osteoporosis is a health concern characterized by reduced bone mineral density (BMD) and increased risk of fragility fractures. Many studies have investigated the association between genetic variants and osteoporosis. Polymorphism and allelic variations in the vitamin D receptor gene (VDR) have been found to be associated with bone mineral density. However, many studies have not been able to find this association. Literature review was conducted in several databases, including MEDLINE/Pubmed, Scopus, EMBASE, Ebsco, Science Citation Index Expanded, Ovid, Google Scholar, Iran Medex, Magiran and Scientific Information Database (SID) for papers published between 2000 and 2013 describing the association between Fok1 and Bsm1 polymorphisms of the VDR gene and osteoporosis risk. The majority of the revealed papers were conducted on postmenopausal women. Also, more than 50% studies reported significant relation between Fok1, Bsm1 and osteoporosis. Larger and more rigorous analytical studies with consideration of gene-gene and gene-environment interactions are needed to further dissect the mechanisms by which VDR polymorphisms influence osteoporosis.

Keywords: Osteoporosis, Vitamin D receptor gene, Bone density, Polymorphism, Fok1, Bsm1

Introduction

The genetic variants of osteoporosis

Bone is a metabolically active tissue that experiences continuous remodeling via two reciprocal processes, bone formation and resorption. Respectively, osteoclasts, osteoblasts and osteocytes are responsible for bone resorption, formation and maintenance [1]. Osteoporosis is a bone disease characterized by low bone density caused by increased activity of osteoclasts and decreased bone turnover [2,3].

The prevalence of osteoporosis varies between different populations and ethnic groups [4-6] for example because of the high degree of ethnic variety in China, different studies show variety prevalence of osteoporosis [7-24]. Considering its high prevalence, the disease imposes a heavy burden on the patients and families as well as the healthcare system. In fact, the numbers of women with osteoporotic fractures are higher than those who experience breast, ovary and uterus cancer [25-27].

Osteoporosis is a disease caused by the interaction of genetic and environmental factors. According to many studies, the contribution of genetic and environmental factors is about 70% and 30% respectively. The environmental factors can control gene expression and accordingly, the process of the disease [28]. The study showed that 60-80% feature of bone mass depends on genetics. The Caucasians and Asians usually have lower bone density values than Negros, Hispanics and Latino Americans [29]. In addition, studies have shown that female offspring of osteoporotic women have lower bone density in comparison with that of those with normal bone density values [30]. Similarly, male offspring of men who are diagnosed with idiopathic osteoporosis have lower BMD in comparison with that of men with normal bone density values [31]. Also, the study of female twins have shown heritability of BMD to be 57% to 92% [32-35].
Different approaches including linkage studies on human and experimental animals as well as candidate gene studies and alterations in gene expression are being used currently to identify the role of genes in this regard [36].

There are many relevant published studies of the genomic susceptibility to osteoporosis. Genes can affect the skeletal system in two ways. The first, control body uptakes and intakes such as urinary calcium excretion to modulate BMD, the second way is poor metabolism due to genetic defects [37].

There calcium absorption pathways consists of transcellular and paracellular. The transcellular pathway closely depends on the action of calcitriol and the intestinal vitamin D receptor. Transcellular transport occurs primarily in the duodenum where the VDR (Vitamin D receptor) is expressed in the highest concentration. So the regulation of VDR gene is most important in high efficiency of calcium absorption [38,39].

Estrogens are known to play an important role in regulating bone homeostasis and preventing postmenopausal bone loss. They act through binding to two different estrogen receptors (ERs), ERα and ERβ, which are members of the nuclear receptor superfamily of ligand-activated transcription factors. Both ER kinds are expressed in osteoblasts, osteoclasts, and bone marrow stromal cells. And also ESRα has a prominent role in regulating bone turnover and the maintenance of bone mass [40,41].

Different studies have reported a list of effective genes on osteoporosis; the most important of which are vitamin D receptor gene (VDR), estrogen receptor alpha (ESRα), interleukin -6 (IL-6), Collagen type I (COLIA1), LDL receptor-related protein 5 (LRP5) [26,42,43].

Over the recent decades, genome-wide association studies (GWAS) have contributed to the understanding of gene structure in complex and chronic diseases such as osteoporosis. Some of studies have indicated 62 significant loci where control bone mineral density variation [27,44-47].

**Candidate genes for BMD**

Candidate gene studies have mainly focused on Vitamin D receptor genes (VDR), type 1 Estrogen receptor genes (ESR1) and type 1 Collagen (Col1) [41,48-50]. In this paper, the more important candidate genes, “VDR,” is discussed.

**Vitamin D receptor gene**

Vitamin D receptor’s (VDR) genotypes have been associated with the development of several bone diseases as well as multiple sclerosis (MS), osteoporosis, and vitamin D-dependent rickets type II and other complex maladies [51].

The human gene encoding the VDR gene has been localized on chromosome 12q12-q14. Vitamin D receptors (VDRs) are members of the NR1I family, which also includes pregnane X (PXR) and constitutive androstane (CAR) receptors, which form heterodimers with members of the retinoid X receptor family [52]. VDR is expressed in the intestine, thyroid and kidney and has a vital role in calcium homeostasis. VDRs repress the expression of 1-alpha-hydroxylase (the proximal activator of 1,25(OH)2D3) and induce the expression of 1,25(OH)2D3 through inactivating the enzyme CYP24. Also, it has recently been identified as an additional bile acid receptor alongside FXR with a protective role in gut against the toxic and carcinogenic effects of these endobiotics [53].

Gene ontology (GO) annotations related to this gene include steroid hormone receptor activity and sequence-specific DNA binding transcription factor activity. An important paralog of this gene is NR4A3 [54].

There are more than 100 restriction endonuclease recognition sites in VDR gene and some of them are polymorphisms such as Fok1, Bsm1, Apa1 and …. Fok1 and Taq1 are located in exon 2 and 9 respectively. And also, Bsm1 and Apa1 are located in intron 8. Bsm1, Apa1 and Taq1 have been identified at the 3′ end of the gene. The effects of VDR gene polymorphisms are in connection with each other [55-57]. In many studies, polymorphisms of VDR gene have been investigated. A relationship between the VDR polymorphism and osteoporosis remain unclear requiring further in depth studies [58,59].

A series of characterized VDR gene polymorphisms, including Fok1, Bsm1, Taq1, and Apa1, have been extensively studied with regard to their association with osteoporosis, but with vise versa results [41,60-63]. Significant associations of Fok1 polymorphism with low BMD have been described in some studies, [64-66] but not in others [67,68].

The Bsm1 restriction enzyme identifies a polymorphic site at an intron at the 3′-end which is in linkage disequilibrium with several other polymorphisms, including Apa1, Taq1, and the variable-length poly(A) [69]. Although functional data have been inconclusive for Bsm1, several small studies evaluating Bsm1 have reported significant associations with osteoporosis [70,71].

To clear the relationship between osteoporosis and VDR gene polymorphisms (Fok1, Bsm1), we review the current evidence systematically.

**Methods**

**Eligibility criteria**

In this systematic review, the studies that had assessed the association between VDR gene polymorphisms and osteoporosis between 2000 and 2013 were included. In all these studies the diagnosis of osteoporosis was performed based on BMD measurement by Dual X-ray
Densitometry (DXA) at least one of the bone sites. All kinds of original studies such as cross-sectional, longitudinal, and case controls were included. All review articles, Meta-analysis and systematic reviews after checking references (to avoid missing any paper), were excluded. Also, the articles performed on patients with secondary osteoporosis as well as non-human studies (cell culture or animal studies) and cellular-molecular discussions were excluded. To avoid language bias non-English-language publications were also included and Google-Translator was used to extract these articles’ data.

**Literature search and data extraction**

The search strategy was based on electronic and hand searching. Main key words in this systematic review were Osteoporosis, Bone density, vitamin D receptor gene, polymorphisms, Fok1 and Bsm1. We searched electronic databases of biological and health sciences including MEDLINE (pubmed), Scopus, EMBASE, Ebsco, Science Citation Index Expanded, Ovid, Google Scholar, Iran Medex, Magiran and Scientific Information Database (SID). All national and international congresses about genetic and osteoporosis like IOF and NOF congresses were examined. And also expert’s curriculum vitae in this field were checked for relevant studies. Subsequently, the searches were carried out and publications of interest were selected, based on titles and abstracts. The full text of all selected publications was assessed for relevance. If the full texts of papers were not available, they were obtained through correspondence with the authors. This was followed by extracting the relevant data from the identified publications according to the steps described in detail.

![Figure 1 Flow diagram of the literature search.](http://www.jdmdonline.com/content/13/1/98)
| First author | Year | Country | Ethnicity | Genotyping method | Design | Total sample size | Osteoporosis Control | SNP |
|--------------|------|---------|-----------|-------------------|--------|------------------|----------------------|-----|
| Wynne, F    | 2002 | Ireland | Irish     | PCR-RFLP         | Case-Control | 511 | 381 | 130 | Fok1 |
| Van Pottelbergh | 2002 | Belgium | Belgium   | PCR-RFLP         | Case-Control | 408 | 271 | 137 | Fok1 |
| Tarner       | 2012 | Turkey  | Turkish   | PCR-RFLP         | Case-Control | 229 | 183 | 46  | Fok1 |
| Jakubowska   | 2012 | Netherlands | Netherlands | PCR-RFLP   | Case-Control | 455 | 161 | 294 | Fok1 |
| Kanan        | 2013 | Jordan  | Jordanian | PCR-RFLP         | Case-Control | 210 | 120 | 90  | Fok1 |
| Zhang        | 2006 | Chinese | Chinese   | PCR-RFLP         | Case-Control | 92  | 26  | 66  | Fok1 |
| Kim, J. G   | 2001 | Korea   | Korean    | PCR-RFLP         | Cross-sectional | 229 | -   | -   | Fok1 |
| Deng, H. W  | 2002 | USA     | Caucasian | PCR-RFLP       | Cross-sectional | 630 | -   | -   | Fok1 |
| Lau, E. M. C | 2002 | China   | Chinese   | PCR-RFLP         | Cross-sectional | 684 | -   | -   | Fok1 |
| Chen, H. Y  | 2002 | Taiwan  | Taiwan    | PCR-RFLP         | Cross-sectional | 163 | -   | -   | Fok1 |
| Strandberg, S. | 2003 | Sweden  | Swedish   | PCR-RFLP         | Cross-sectional | 88  | -   | -   | Fok1 |
| Rabon-Stith, K. | 2005 | USA (Maryland) | USA (Maryland) | PCR-RFLP | Cross-sectional | 206 | -   | -   | Fok1 |
| Cusack, S.  | 2006 | Denmark | Danish    | PCR-RFLP         | Cross-sectional | 224 | -   | -   | Fok1 |
| Terpstra     | 2006 | Netherlands | Netherlands | PCR-RFLP   | Cross-sectional | 120 | -   | -   | Fok1 |
| Lau, H. H. L | 2006 | China   | southern Chinese | PCR-RFLP | Cross-sectional | 674 | -   | -   | Fok1 |
| Falchetti, A. | 2007 | Italy  | Italian   | PCR-RFLP         | Cross-sectional | 424 | -   | -   | Fok1 |
| Han, X.      | 2009 | China   | Han       | PCR-RFLP         | Cross-sectional | 100 | -   | -   | Fok1 |
| Hosseinnejad | 2009 | IRAN    | IRAN      | PCR-RFLP         | Cross-sectional | 205 | -   | -   | Fok1 |
| Hosseinnejad | 2009 | IRAN    | IRAN      | PCR-RFLP         | Cross-sectional | 312 | -   | -   | Fok1 |
| Ozaydin      | 2010 | Turkey  | Turkish   | PCR-RFLP         | Cross-sectional | 88  | -   | -   | Fok1 |
| Galbav       | 2010 | Slovakia | Slovak    | PCR-RFLP         | Cross-sectional | 121 | -   | -   | Fok1 |
| Perez, A.    | 2008 | Argentina | Cordoba   | PCR-RFLP         | Case-Control | 176 | 108 | 68  | Bsm1 |
| Fontova, R.  | 2000 | Spain   | Spanish   | PCR-RFLP         | Case-Control | 156 | 105 | 51  | Bsm1 |
| Uysal, A. R. | 2008 | Turkey  | Turkish   | PCR-RFLP         | Case-Control | 246 | 100 | 146 | Bsm1 |
| Eckstein     | 2002 | Israel  | Jewish Israeli | PCR-RFLP | Case-Control | 324 | 86  | 238 | Bsm1 |
| Borjas-Fajardo, L | 2003 | Spain | Spanish    | PCR-RFLP         | Case-Control | 133 | 78  | 55  | Bsm1 |
| DurusuTanriover, M. | 2010 | Turkey | Turkish   | PCR-RFLP         | Case-Control | 100 | 50  | 50  | Bsm1 |
| Chen, J.     | 2003 | China   | Chinese   | PCR-RFLP         | Case-Control | 61  | 40  | 21  | Bsm1 |
| Tamulaitien  | 2012 | Lithuania | Lithuania | PCR-RFLP   | Case-Control | 73  | 28  | 45  | Bsm1 |
| Nelson       | 2000 | USA     | African-American | PCR-RFLP | Cross-sectional | 43  | -   | -   | Bsm1 |
| Sowińska     | 2000 | Poland  | Polish    | PCR-RFLP         | Case-Control | 88  | 40  | 48  | Bsm1 |
| Chen, H.Y    | 2001 | China   | Chinese   | PCR-RFLP         | Cross-sectional | 171 | -   | -   | Bsm1 |
| Pollak, R. D | 2001 | Israeli | Israeli   | PCR-RFLP         | Cross-sectional | 634 | -   | -   | Bsm1 |
| Kubota, M.   | 2001 | Japan   | Japanese  | PCR-RFLP         | Cross-sectional | 126 | -   | -   | Bsm1 |
| Laaksonen, M. | 2002 | Finland | Finish    | PCR-RFLP         | Cross-sectional | 93  | -   | -   | Bsm1 |
| van der Sluis, L. | 2003 | Netherlands | Caucasian | PCR-RFLP   | Cross-sectional | 148 | -   | -   | Bsm1 |
| Grundberg    | 2003 | Sweden  | Swedish   | PCR-RFLP         | Cross-sectional | 343 | -   | -   | Bsm1 |
| Kammerer, C. M. | 2004 | Mexico  | Mexican American | PCR-RFLP | Cross-sectional | 471 | -   | -   | Bsm1 |
| Seremak-Mrozikiewicz, A | 2004 | Poland | Polish    | PCR-RFLP         | Cross-sectional | 34  | -   | -   | Bsm1 |
| Palomba, S.  | 2005 | Italy   | Italian   | PCR-RFLP         | Cross-sectional | 1100 | - | - | Bsm1 |
| Dong, J.     | 2006 | China   | Han       | PCR-RFLP         | Cross-sectional | 90  | -   | -   | Bsm1 |
| Bernardes    | 2005 | Portugal | Portuguese | PCR-RFLP | Cross-sectional | 114 | -   | -   | Bsm1 |
below. Totally, two reviewers reviewed the articles. In case of disagreement, the third reviewer assessed the articles.

The following data were extracted from each published article: name of the first author, publication year, the number of case and control by gender, the number of menopausal women, and the number of performed BMDs, ethnic origin of the studied population, mean age, genotyping method (PCR-RFLP and TaqMan), Bone sites, and the genotype frequency of the polymorphisms. The reliability of data extraction forms was assessed by genetics and endocrinology specialists. And the content validity was assessed by 10 articles and was confirmed by 0.75 Cronbach’s Alpha. Methodological quality, the strength and weaknesses of included studies were investigated using a modified STROBE checklist.

Results and discussion
Baseline characteristics
A schematic of the literature search is shown in Figure 1. According to the inclusion/exclusion criteria eligibility, 61 articles were identified regarding the associations between the Fok1 and Bsm1 polymorphisms of VDR gene and osteoporosis risk. Among these studies, 21 studies concerned the association of the Fok1 polymorphism with osteoporosis [9,72-91], while 26 studies investigated the association between Bsm1 polymorphism and osteoporosis risk [92-117]. Also 14 articles evaluated both polymorphism associations with osteoporosis [118-131]. All of these 61 studies provided sufficient data to calculate the possible relationship between the two polymorphisms of the VDR gene and osteoporosis risk. The general characteristics of the selected studies are summarized in Table 1.

In these studies, diverse groups of people were discussed. 36.5% of the studies studied postmenopausal women. On the other hand, post-menopausal and pre-menopausal woman were studied simultaneously in 22.2% of the articles and 12.7% of them studied all groups. According to the results, 96.8% of studies performed the polymorphisms using PCR-RFLP “polymerase chain reaction- restriction fragment length polymorphism”. The other methods such as Taq-man were used to determine the association between Bsm1 and Fok1 polymorphisms and osteoporosis.

As mentioned above, the studies after year 2000 on world were enrolled in this systematic review. Most articles were published in 2006 and after that the number of papers showed a decline trend.

Based on articles, totally 17473 persons studied. 65.9% of studies reported a significant relation between Bsm1 and osteoporosis risk. Likewise, 60.0% of studies reported a significant relation between Fok1 and osteoporosis risk.

Also, the papers were categorized by gender and age. The data indicated that most of the articles were done on women and also on older ages. Most of studies were examined post menopausal women.

Table 1 Characteristics of studies included in the systematic review (Continued)

| Study | Year | Country | Ethnicity | Genotyping Method | Study Design | Sample Size | Gender | Age | Site | Genotype Frequency |
|-------|------|---------|-----------|------------------|--------------|-------------|--------|-----|------|-------------------|
| Mitra, S. [113] | 2006 | India | Indian | PCR-RFLP | Cross-sectional | 246 | - | - | Bsm1 | 
| Bezerra [114] | 2008 | Brazil | Brazilian | PCR-RFLP | Cross-sectional | 40 | - | - | Bsm1 | 
| Musumeci [115] | 2009 | Italy | Sicilian | PCR-RFLP | Cross-sectional | 360 | - | - | Bsm1 | 
| Stathopoulou, M. G. [116] | 2011 | Greece | Greek | PCR-RFLP | Cross-sectional | 578 | - | - | Bsm1 | 
| Poursmaeili [117] | 2013 | IRAN | IRAN | PCR-RFLP | Cross-sectional | 146 | - | - | Bsm1 | 
| Horst - Sikorska, W. [118] | 2007 | Poland | Polish | PCR-RFLP | Cross-sectional | 279 | - | - | Both | 
| Gonzalez [119] | 2013 | Mexico | Mexican-Mestizo | TaqMan | Case-Control | 320 | 232 | 88 | Both | 
| Kanan, R. M. [120] | 2008 | Jordan | Jordanian | PCR-RFLP | Case-Control | 230 | 150 | 80 | Both | 
| Lisker, R [121] | 2003 | Mexico | Mexican | PCR-RFLP | Case-Control | 122 | 65 | 57 | Both | 
| Mansour, L. [122] | 2010 | Egypt | Egyptian | PCR-RFLP | Case-Control | 70 | 50 | 20 | Both | 
| Rogers [123] | 2000 | no indicated | no indicated | PCR-RFLP | Cross-sectional | 46 | - | - | Both | 
| Lorentzon [124] | 2001 | Sweden | Caucasian | PCR-RFLP | Cross-sectional | 99 | - | - | Both | 
| Zajíčková [125] | 2002 | Czech | Czech | PCR-RFLP | Cross-sectional | 114 | - | - | Both | 
| Vidal, C. [126] | 2003 | Malta | Malta | PCR-RFLP | Cross-sectional | 104 | - | - | Both | 
| Bandrés [127] | 2005 | Spain | Caucasian | PCR-RFLP | Cross-sectional | 177 | - | - | Both | 
| Ivanova, J. [128] | 2006 | Bulgaria | Bulgarian | PCR-RFLP | Cross-sectional | 219 | - | - | Both | 
| Macdonald, H. M [129] | 2006 | UK | Scotland | PCR-RFLP | Cross-sectional | 3100 | - | - | Both | 
| Yavuz [130] | 2007 | Turkey | Turkish | PCR-RFLP | Case-Control | 206 | 381 | 130 | Both | 
| Sanwalka [131] | 2013 | India | Indian | PCR-RFLP | Case-Control | 120 | 271 | 137 | Both |
After characterization of authors' countries, it was demonstrated that respectively, China [9,77,85,87,98,102] and Turkey [74,90,94,97,130] presented 6 and 5 studies and identified as most active countries in such researches.

In conclusion, both gender and ethnicity are effective factors on osteoporosis and bone mineral density.

As is evident, genetic variant has a tremendous role to adjust bone activities and therefore along with vitamin D deficiency, has a large effect on osteoporosis incidence and also osteoporotic fractures. In this systematic review, due to study the association between low bone density and Bsm1 and Fok1 polymorphisms, 61 papers were studied and statistically analyzed. As a main result, most of the studies were performed on post-menopausal women i.e. the largest risk group to their major content of research [132]. It seems that it is necessary to evaluate the association of genetic variant for lower age groups of both genders. Accordingly, genetic testing can be used to prevent osteoporosis and low bone density.

In more than 50% of studies a significant association was found between the two polymorphisms (Fok1 and Bsm1) and osteoporosis. Based on the articles, 65.9% of studies reported a significant correlation between Bsm1 and osteoporosis risk. Likewise, 60.0% of studies reported a significant correlation between Fok1 and osteoporosis risk. Most of the studies were performed in developed countries but also, developing countries have initiated this way.

An important and noticeable issue in this systematic review is different results in different races [44,133]. Ethnicity and race, like gender, can influence the epidemiology of osteoporosis and BMD. Some of studies indicate that lowest BMD shown in white women and also, bone mineral density is higher in African Americans [134,135].

In more that 95% studies for assessing polymorphisms, PCR-RFLP were used (Table 1). It is noteworthy; Taq-Man PCR-RFLP were used (Table 1). It is noteworthy; Taq-Man [134,135].

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
This Article comes from Thesis. Obviously, to provide a systematic review, according to the standards, several experts should participate to review the articles and two different persons should check the excluded data, and a third reviewer should recheck all of these procedures. All authors contributed in these steps. All authors read and approved the final manuscript.

Author details
1 Department of biology, Damghan branch, Islamic Azad University, Damghan, Iran. 2 Osteoporosis Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. 3 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. 4 Biomedical Engineering Department, Maziar University, Rouyan, Iran. 5 Non-communicable Disease Department, Iran Ministry of Health and Medical Education, Tehran, Iran. 6 Dental Implant Research Center, Tehran University of Medical Sciences, Tehran, Iran. 7 EMRI, Dr Shariati Hospital, North Keregar St., Tehran 14114, Iran.

Received: 21 August 2014 Accepted: 30 September 2014
Published online: 17 October 2014

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