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Association Between Vitamin D Levels and Vitamin D Receptor *FokI* Polymorphism in Thai Postmenopausal Women With Osteoporosis

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Background: Osteoporosis is a complex genetic disease, which is common among postmenopausal women. It is characterized by decreased bone mineral density (BMD) and increased bone fragility and fractures.

Objective: To study the association between serum vitamin D levels and vitamin D receptor (VDR) genetic *FokI* polymorphism in postmenopausal women with osteoporosis.

Methods: A total of 60 postmenopausal women who came for treatment at the menopausal clinic at Ramathibodi Hospital were enrolled. All of the patients had their BMD measured, and were determined serum vitamin D levels and VDR *FokI* polymorphism. Data were analyzed using chi-square and Fisher exact tests. The frequency of single nucleotide polymorphism (SNP) with risk of osteoporosis was compared.

Results: Among 60 postmenopausal women, 26 (43.3%) women were an osteoporotic group and 34 (56.7%) women were non-osteoporotic group. There were no significant differences in age, vitamin D levels, or VDR *FokI* polymorphism between the groups ($P > .05$). However, the TT genotype of VDR *FokI* polymorphism was significantly associated with vitamin D deficiency (< 20 ng/mL) (OR, 6.15; 95% CI, 1.51 - 25.14; $P < .05$).

Conclusions: Vitamin D levels and genotype of VDR *FokI* polymorphisms were similar between the osteoporotic and non-osteoporotic postmenopausal women. The TT genotype of VDR *FokI* polymorphism showed a significant association with vitamin D deficiency. Therefore, TT genotype of VDR *FokI* polymorphism may be used to predict risk of vitamin D deficiency.

Keywords: Osteoporosis, Postmenopausal, Vitamin D levels, Vitamin D receptor, *FokI* polymorphism

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Introduction

Osteoporosis, characterized by decreased bone mineral density (BMD) and increased bone fragility and fracture risk, is prevalent within the aging population. It is particularly common among postmenopausal women and is becoming a major public health issue. The World Health Organization (WHO) estimates that 200 million women and men suffer from osteoporosis worldwide. In the United States and the European Union, approximately 30% of all postmenopausal women have osteoporosis, with 40% predicted to suffer one or more fragility fractures during their remaining lifetime.[1] Several environmental factors have been identified as risk factors for osteoporosis, including exercise and calcium intake. In addition, twin and family studies have demonstrated about 50% to 85% heritability of osteoporosis in the general population can be attributed to the genetic factors,[2] thus playing a key role its development.

Osteoporosis is 3 times more common in women than in men, partly due to women having a lower peak bone mass and the hormonal changes that occur at menopause. Estrogens have an important function in preserving bone mass during adulthood, and bone loss occurs as levels decline, usually at approximately 50 years of age. Moreover, women tend to live longer than men and therefore have greater reductions in bone mass.[3]

In 1990, an estimated 1.3 to 1.7 million hip fractures were recorded worldwide,[4, 5] with this number expected to increase to almost 3 million in 2025. This is likely an underestimation, since in many regions, hip fracture rates have increased even after age has been taken into consideration.[5]

Using the Thai BMD reference, the age specific prevalence of osteoporosis among Thai women has risen progressively with increasing age (> 50% after the age of 70 years). The age adjusted prevalence of osteoporosis has been observed to increase progressively at the lumbar spine (19.8%), femoral neck (13.6%), and intertrochanteric (10%), indicating the magnitude of the condition in the population. The prevalence of osteoporosis is associated with advanced age and duration after menopause.

Vitamin D plays a central role in bone formation and remodeling.[6, 7] While several studies have documented the importance of maintaining adequate levels of serum vitamin D to protect against bone fracture,[8] vitamin D deficiency remains a major worldwide health concern.[6, 9, 10] For example, despite the Middle East countries enjoying sunshine all year round, their populations suffer from significant vitamin D deficiency across all ages; possessing one of the highest rates of rickets in the world.[11] Recently, vitamin D deficiency in the Saudi Arabian population, reached 41% to 64% among young females aged 12 to 18 years.[12] Several factors contribute to the development of vitamin D deficiency and its negative physiological impact on bones, including decreased dietary intake, inadequate production of the vitamin in the skin, and disturbances in the production of the active hormonal form of vitamin D.[7, 13] In addition to vitamin D status, mutations in the vitamin D receptor markedly contribute to the complications of vitamin D deficiency in relation to bone health.[14] In Thailand, the prevalence of vitamin D deficiency is reported to be 60.2% in postmenopausal women.[15]

Vitamin D receptor (VDR) is a transcription factor regulating the expression of genes that mediate its biologic activity. VDR is a member of a rather large family of nuclear hormone receptors that includes the receptors for glucocorticoids, mineralocorticoids, sex hormones, thyroid hormone, and vitamin A metabolites or retinoids. VDR is widely distributed, and is not restricted to those tissues considered the classic target tissues of vitamin D.[16]

VDR is the target receptor to regulate the transcription of vitamin D, and is thought to play a key role in cellular differentiation and proliferation.[16] Recently, VDR gene polymorphisms, such as *ApaI, BsmI*, *Cdx2*, *TaqI*, and *FokI,* have gained greater attention, as studies have verified their association with several diseases.[17] This has led to interest being directed towards the relationship between VDR gene polymorphisms and BMD and osteoporosis risk in postmenopausal women.

The VDR gene polymorphisms are located on the long arm of chromosome 12 (12q13.11), a member of the nuclear receptor superfamily. A number of studies have shown that VDR gene polymorphisms, including *FokI*, play an important role in the pathogenesis of osteoporosis.[18] It has been shown that DNA extracted by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), results in VDR *FokI* polymorphism expected fragments of 266 bp in the CC genotype; 184 bp and 63 bp in the TT genotype; and 266 bp, 184 bp, and 63 bp in the CT genotype, respectively.[19]

The association between osteoporosis and VDR *FokI* polymorphism has been widely studied. Previous study from Techapatiphandee et al[19] found that the TT genotype was significantly associated with lower BMD and a greater risk of osteoporosis compared with the CC and CT genotypes. However, there are few studies, which have investigated the association between osteoporosis and vitamin D levels and VDR in Thai postmenopausal women. Therefore, this study aimed to investigate the association between vitamin D levels and VDR *FokI* polymorphism and osteoporosis among Thai postmenopausal women.

Methods

Study Design and Participants

This research was an analytical study of vitamin D levels and VDR *FokI* polymorphism among Thai postmenopausal women. A total of 60 women who attended for treatment at the postmenopausal clinic, Ramathibodi Hospital from May 2013 to January 2014, were recruited to take part in this investigation. All patients were screened via assessing their medical history, physical examination and blood testing and had their BMD measured. The patients had their BMD status confirmed by orthopedic physicians and were subsequently divided into osteoporotic and non-osteoporotic groups.

Serum Vitamin D Measurement

Serum 25-hydroxyvitamin D [25(OH)D] was analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS) with an Agilent 1200 Infinity liquid chromatograph (Agilent Technologies, California, USA) coupled to a QTRAP® 5500 tandem mass spectrometer (SCIEX, Illinois, USA) using a MassChrom® 25-OH-Vitamin D3/D2 diagnostics kit (ChromSystems, Munich, Germany). The summation of serum 25-hydroxyvitamin D2 [25(OH)D2] and serum 25-hydroxyvitamin D3 [25(OH)D3] was used to reflect vitamin D status. The total serum 25(OH)D level inter-assay and intra-assay coefficients of variation were 6.3% and 5.0%, respectively.

PCR-RFLP for Genotype of Vitamin D Receptor *FokI* Polymorphism

Blood samples were centrifuged to obtain the buffy coat (1000 x g for 10 minutes at room temperature). Genomic DNA was extracted from the buffy coat fraction by phenol/chloroform extraction.

DNA was extracted and assessed for the *FokI* (rs2228570) genotype by PCR-RFLP. Genomic DNA served as a template for amplification of exon 2 with the primers sequence, (forward: 5′-ACCAAGGATGCCAGCTGG-3′ and reverse: 5′-TTGTACCCTGCCCGCAAGAAA-3′, with annealing temperature at 45 °C).

Statistical Analysis

The allele and genotype frequency were compared between osteoporotic and non-osteoporotic postmenopausal women. The differences between groups were examined using chi-square and Fisher exact tests, with the significance level set at $P < .05$. Odds ratio (OR), 95% confidence interval (CI) and P value were used as parameters to compare the frequency of single nucleotide polymorphisms (SNP) with the risk of vitamin D level and vitamin D deficiency. The Statcalc Program (AcaStat Software, Leesburge, VA, USA) was used to perform all statistical analysis.

Ethics

This study was approved by the Human Research Ethics Committee of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (No. MURA2016/128, on February 29, 2016).

Results

A total of 26 (43.3%) women were allocated to the osteoporotic group and 34 (56.7%) women to the non-osteoporotic group. Mean age was 63 years, with 23 (38.3%) women aged between 61 years and 70 years. Mean (standard deviation, SD) of vitamin D level across both groups was 23.19 (5.52) ng/mL. The majority of postmenopausal women (65.0%) had vitamin D levels between 20ng/mL and 30 ng/mL, with 23.3% having vitamin D levels less than 20 ng/mL, and 11.7% having vitamin D levels more than 30 ng/mL. The vitamin D level was similar between the non-osteoporotic and osteoporotic groups (mean [SD], 24.14 [5.47] ng/mL and 21.95 [5.46] ng/mL, respectively). The most common genotype of VDR *FokI* polymorphism was the CT genotype (46.7%), followed by CC genotype (35.0%) and TT genotype (18.3%), respectively. The frequency of allele C and allele T was 0.583 and 0.417, respectively. In the osteoporotic group, it was found that 63.6% possessed the TT genotype, 38.1% had the CC genotype, and 39.3% had the CT genotype. In the non-osteoporotic group, it was found that only 36.4% had the TT genotype, 60.7% had the CT genotype, and 61.9% had the CC genotype. However, the TT genotype was similar between the osteoporotic and non-osteoporotic groups (Table 1).

There were no significant associations between age, vitamin D levels, genotypes alleles of VDR *FokI* polymorphism and osteoporosis (Table 2).

There was no significant association between age and vitamin D levels (Table 3).

Table 1. Distribution of Age, Vitamin D Level, and VDR *FokI* Polymorphism in the Osteoporotic and Non-Osteoporotic Groups

Classification	No. (%)		
	Osteoporosis (n = 26)	Non-Osteoporosis (n = 34)	Total (N = 60)
Age, y			
41 - 50	4 (57.1)	3 (42.9)	7 (11.7)
51 - 60	6 (31.6)	13 (68.4)	19 (31.7)
61 - 70	12 (52.2)	11 (47.8)	23 (38.3)
71 - 80	4 (40.0)	6 (60.0)	10 (16.7)
81 - 90	0 (0.0)	1 (100.0)	1 (1.7)
Mean (SD)	63.04 (8.65)	63.21 (9.51)	63.13 (9.07)
Vitamin D level, ng/mL			
< 20	8 (57.1)	6 (42.9)	14 (23.3)
20 - 30	16 (41.0)	23 (59.0)	39 (65.0)
> 30	2 (28.6)	5 (71.4)	7 (11.7)
Mean (SD)	21.95 (5.46)	24.14 (5.47)	23.19 (5.52)
Genotypes of *FokI*			
CC	8 (38.1)	13 (61.9)	21 (35.0)
CT	11 (39.3)	17 (60.7)	28 (46.7)
TT	7 (63.6)	4 (36.4)	11 (18.3)

Abbreviation: SD, Standard deviation.

Table 2. Association Between Age, Vitamin D Level, and VDR *FokI* Polymorphism in the Osteoporotic and Non-Osteoporotic Groups

Classification	No. (%)			*P* Value*	OR (95% CI)
	Osteoporosis (n = 26)	Non-Osteoporosis (n = 34)	Total (N = 60)		
Age, y					
≤ 60	10 (38.5)	16 (61.5)	26 (43.3)	.51	1.42 (0.50 - 4.02)
> 60	16 (47.1)	18 (52.9)	34 (56.7)		
Vitamin D level, ng/mL					
< 20	8 (57.1)	6 (42.9)	14 (23.3)	.23	2.07 (0.62 - 6.98)
≥ 20	18 (39.1)	28 (60.9)	46 (76.7)		
Genotypes of *FokI*					
CC $^{+}$	8 (38.1)	13 (61.9)	21 (35.0)	.55	0.72 (0.24 - 2.12)
CC $^{-}$	18 (46.2)	21 (53.8)	39 (65.0)		
CT $^{+}$	11 (39.3)	17 (60.7)	28 (46.7)	.55	0.73 (0.26 - 2.05)
CT $^{-}$	15 (46.9)	17 (53.1)	32 (53.3)		
TT $^{+}$	7 (63.6)	4 (36.4)	11 (18.3)	.18[a]	2.76 (0.71 - 10.73)
TT $^{-}$	19 (38.8)	30 (61.2)	49 (81.7)		
Allele C of *FokI*					
C $^{+}$	27 (38.6)	43 (61.4)	70 (58.3)	.21	0.63 (0.30 - 1.31)
C $^{-}$	25 (50.0)	25 (50.0)	50 (41.7)		
Allele T of *FokI*					
T $^{+}$	25 (50.0)	25 (50.0)	50 (41.7)	.21	1.59 (0.75 - 3.32)
T $^{-}$	27 (38.6)	43 (61.4)	70 (58.3)		

Abbreviations: CI, confidence interval; OR, odds ratio.

* The differences between groups were examined using chi-square and Fisher exact teste, with the significance level set at $P < .05$.

[a] Fisher's exact test.

+ Presence of genotype and allele.

- Absence of genotype and allele.

Table 3. Association Between Age and Vitamin D Level

Age, y	No. (%)			*P* Value*	OR (95% CI)
	Vitamin D Level, mg/mL		Total (N = 60)		
	< 20 (n = 14)	≥ 20 (n = 46)			
≤ 60	8 (30.8)	18 (69.2)	23 (43.3)	.23	0.48 (0.14 - 1.62)
> 60	6 (17.6)	28 (82.4)	31 (56.7)		

Abbreviations: CI, confidence interval; OR, odds ratio.

* *P* value < .05 was considered statistically significant.

There was no significant association between age, genotypes, and alleles of VDR *FokI* polymorphism (Table 4).

The TT genotype of VDR *FokI* polymorphism was significantly associated with vitamin D deficiency ($P < .05$) The presence of genotype TT group was more prevalent with vitamin D deficiency (vitamin D < 20 ng/mL) compared with the absence of genotype TT group (54.5% and 16.3%; $P < .05$). The presence of genotype TT group had 6.15 times greater odds risk of vitamin D deficiency compared with the absence of genotype TT group (95% CI, 1.51 - 25.14). The other genotypes and alleles were not significantly associated with vitamin D levels (Table 5).

Table 4. Association Between Age and Genotype of *FokI* Polymorphism

Genotypes of *FokI*	No. (%)			*P* Value*
	Age, y		Total (N = 60)	
	> 60 (n = 34)	≤ 60 (n = 26)		
CC	11 (52.4)	10 (47.6)	21 (35.0)	.50
CT	18 (64.3)	10 (35.7)	28 (46.7)	
TT	5 (45.5)	6 (54.5)	11 (18.3)	

* *P* value < .05 was considered statistically significant.

Table 5. Association Between Genotypes and Alleles of *FokI* Polymorphism and Vitamin D Levels

Classification	No. (%)			*P* Value*	OR (95% CI)
	Vitamin D Level ng/mL		Total (N = 60)		
	< 20 (n = 14)	≥ 20 (n = 46)			
Genotypes of *FokI*					
CC +	4 (19.0)	17 (81.0)	21 (35.0)	.75[a]	0.68 (0.19 - 2.52)
CC -	10 (28.6)	29 (74.4)	39 (65.0)		
CT +	4 (14.3)	24 (85.7)	28 (46.7)	.12	0.37 (0.10 - 1.34)
CT -	10 (31.3)	22 (68.8)	32 (53.3)		
TT +	6 (54.5)	5 (45.5)	11 (18.3)	.01[a]	6.15 (1.51 - 25.14)
TT -	8 (16.3)	41 (83.7)	49 (81.7)		
Allele C of *FokI*					
C +	12 (17.1)	58 (82.9)	70 (58.3)	.06	0.44 (0.19 - 1.04)
C -	16 (32.0)	34 (68.0)	50 (41.7)		
Allele T of *FokI*					
T +	16 (32.0)	34 (68.0)	50 (41.7)	.06	2.28 (0.96 - 5.38)
T -	12 (17.1)	58 (82.9)	70 (58.3)		

Abbreviations: CI, confidence interval; OR, odds ratio.

* The differences between groups were examined using chi-square and Fisher exact teste, with the significance level set at $P < .05$.

[a] Fisher's exact test.

+ Presence of genotype and allele.

- Absence of genotype and allele.

Discussion

Osteoporosis is a common complex bone disease in postmenopausal women, which is characterized by decreased BMD and increased bone fragility and fractures. Several environmental factors have been identified as risk factors for osteoporosis, including age, exercise, calcium intake, vitamin D levels, vitamin D receptors, and genetics.

Since vitamin D plays a central role in bone formation and remodeling, it is important to maintain adequate levels of serum vitamin D to protect against bone fractures. This study found that the majority of postmenopausal women had low vitamin D levels. Whilst higher vitamin D values were generally observed in the non-osteoporotic patients, the differences in vitamin D levels between the osteoporotic and non-osteoporotic groups were not statistically significant.

Our results contrast with previous studies of vitamin D status in postmenopausal women at Srinagarind Hospital in Khon Kaen, Thailand,[15] and King Fahd University Hospital, Saudi Arabia.[20] These studies demonstrated significant positive correlations between vitamin D levels and BMD. The disparity between our findings may be due to the differences in the study population and/or the sample size. In addition, our study used a threshold of vitamin D deficiency (< 20 ng/mL) based on a study from Romania,[21] which found a higher prevalence of vitamin D deficiency (74.8%) compared with our present study (23.3%).

Vitamin D deficiency is currently a major worldwide health concern worldwide, with Middle Eastern countries particularly suffering from significant vitamin D deficiency across all ages. Bassil et al[22] studied vitamin D deficiency in the Middle East and North Africa regions, reporting that rickets and osteomalacia still occur despite high levels of sunlight exposure. Vitamin D deficiency still prevailed, with rates varying 30% to 90%, when using the desirable serum 25-hydroxyvitamin D threshold of less than 20 ng/mL. Advancing age, female gender, multiparity, clothing style, season, socioeconomic status, and urban living were all recognized predictors of vitamin D deficiency in the adult population.

In the present study, we observed that age had no significant association with vitamin D deficiency. Our findings are not in agreement with a study by Gallagher et al[23] who reported aging to affects vitamin D metabolism and reduces the nutritional status in elderly women. Moreover, our findings contrast with work by Smotkin-Tangorra et al[24] who reported vitamin D insufficiency was significantly associated with increased age. As abovementioned, our findings may differ due to differences between our sample sizes.

Vitamin D plays a crucial role in calcium and phosphate homeostasis and skeletal metabolism. Furthermore, the vitamin D receptor plays an important role in cellular differentiation and the control of proliferation in a variety of cell types. Many studies have shown that VDR gene polymorphisms play an important role in the pathogenesis of osteoporosis, such as *ApaI, BsmI*, *Cdx2*, *TaqI*, and *FokI*.[25]

In this study, the most prevalent genotype of *FokI* polymorphism was the CT genotype, followed by the CC and TT genotypes respectively. It was found that the TT genotype of *FokI* polymorphism had a significant association with vitamin D deficiency. The TT genotype had a 6.15 higher odds risk of vitamin D deficiency (< 20 ng/mL) compared with the CC and CT genotypes.

Our findings are in accordance with the study of Tuncel et al[26] who found that the allele T of *FokI* polymorphism was related to significantly low serum vitamin D levels in the population. Nevertheless, our study found no significant association between TT genotype and osteoporosis, thus contradicting studies undertaken in France,[27] Korea,[28] North India,[29] and Thailand.[19] All of these previous studies concluded that VDR *FokI* polymorphism might be a potential molecular biomarker for the development of osteoporosis, suggesting that the TT genotype of *FokI* is a potential risk factor of osteoporosis. The differences between our results may again be related to our small sample size.

Conclusions

Vitamin D levels and genotype of VDR *FokI* polymorphism were not significantly different between osteoporotic and non-osteoporotic postmenopausal women. The TT genotype of VDR *FokI* polymorphism showed a significant association with vitamin D deficiency. Therefore, the TT genotype of VDR *FokI* polymorphism may be used to predict risk of vitamin D deficiency.

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ความสัมพันธ์ระหว่างระดับวิตามินดีและยีนตัวรับวิตามินดีที่ภาวะพหุสัณฐาน *FokI* กับความหนาแน่นของมวลกระดูกในสตรีไทยวัยหมดประจำเดือน

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บทนำ: โรคกระดูกพรุนเป็นโรคทางพันธุกรรมของสตรีวัยหมดประจำเดือนที่ซับซ้อน มีลักษณะความหนาแน่นของมวลกระดูกลดต่ำลงจนอาจเกิดภาวะกระดูกเปราะและหักได้ง่ายกว่าปกติ

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ระหว่างระดับวิตามินดีและยีนตัวรับวิตามินดีที่ภาวะพหุสัณฐาน *FokI* กับโรคกระดูกพรุน

วิธีการศึกษา: กลุ่มตัวอย่างสตรีไทยวัยหมดประจำเดือน จำนวน 60 คน ที่มารับการตรวจรักษาที่คลินิกวัยหมดประจำเดือน โรงพยาบาลรามาธิบดี ทุกคนได้รับการตรวจความหนาแน่นของมวลกระดูก และได้รับการเจาะเลือดตรวจวัดระดับวิตามินดีและยีนตัวรับวิตามินดี จากนั้นวิเคราะห์ข้อมูลความสัมพันธ์ของตัวแปรโดยใช้สถิติ Chi-square test และสถิติ Fisher exact test และเปรียบเทียบความแตกต่างของสนิปส์ (Single nucleotide polymorphism, SNP) ต่อความเสี่ยงของการเกิดโรคกระดูกพรุน

ผลการศึกษา: กลุ่มตัวอย่างสตรีไทยวัยหมดประจำเดือน จำนวน 60 คน แบ่งเป็นกลุ่มที่เป็นโรคกระดูกพรุน จำนวน 26 คน (ร้อยละ 43.3) และกลุ่มที่ไม่มีภาวะกระดูกพรุน จำนวน 34 คน (ร้อยละ 56.7) ระดับวิตามินดีในกลุ่มที่ไม่มีภาวะกระดูกพรุนสูงกว่ากลุ่มที่เป็นโรคกระดูกพรุน แต่ไม่มีนัยสำคัญ ($P > .05$) เช่นเดียวกันกับอายุและยีนตัวรับวิตามินดีที่ภาวะพหุสัณฐาน *FokI* เมื่อศึกษาความสัมพันธ์ของระดับของวิตามินดีกับยีนตัวรับวิตามินดีที่ภาวะพหุสัณฐาน *FokI* พบว่า จีโนไทป์ TT มีความสัมพันธ์ต่อระดับของวิตามินดี โดยผู้ที่มีจีโนไทป์ TT จะมีภาวะของการขาดวิตามินดี (ระดับวิตามินดีน้อยกว่า 20 นาโนกรัมต่อมิลลิลิตร) มากกว่าผู้ที่มีจีโนไทป์แบบอื่นๆ อย่างมีนัยสำคัญ (OR, 6.15; 95% CI, 1.51 - 25.14; $P < .05$)

สรุป: ระดับวิตามินดีและจีโนไทป์ของยีนตัวรับวิตามินดีที่ภาวะพหุสัณฐาน *FokI* ไม่แตกต่างกันในสตรีที่มีหรือไม่มีภาวะกระดูกพรุน แต่จีโนไทป์ TT ของยีนตัวรับวิตามินดีที่ภาวะพหุสัณฐาน *FokI* มีความสัมพันธ์อย่างมีนัยสำคัญกับระดับวิตามินดี ดังนั้น จีโนไทป์ TT ของยีนตัวรับวิตามินดีที่ภาวะพหุสัณฐาน *FokI* อาจจะใช้ทำนายความเสี่ยงของการเกิดภาวะของการขาดวิตามินดีได้

คำสำคัญ: โรคกระดูกพรุน วัยหมดประจำเดือน ระดับวิตามินดี ยีนตัวรับวิตามินดี ภาวะพหุสัณฐาน *FokI*

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