Received: 3 September 2018 | Accepted: 7 May 2019

DOI: 10.1002/jcb.29135

Journal of Cellular Biochemistry WILEY

RESEARCH ARTICLE

Vitamin D receptor gene polymorphism is associated with multiple myeloma

Hongbing Rui | **Ying Liu** | **Meiying Lin** | **Xiaoqiang Zheng**

Department of Hematology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China

Correspondence
Hongbing Rui, Department of Hematology, The First Affiliated Hospital of Fujian Medical University, No. 20, Chazhong Road, Taijiang District, 350005 Fuzhou, China.
Email: hongbingrui@126.com

Funding information
The Leading Project Funds of The Science and Technology Office of Fujian Province

Abstract

Objectives: The aim of this study was to explore the Vitamin D receptor (*VDR*) gene polymorphism and its association with multiple myeloma (MM) development.

Methods: The peripheral blood of 40 MM cases and 84 healthy controls were collected. Polymerase chain reaction (PCR) and DNA sequencing were applied to detect *VDR* gene polymorphism (including: FokI, BsmI, ApaI, and TaqI). SHESIS biological information software was used to analyze genotypes, alleles, linkage disequilibrium (LD), haplotype distribution, and their association with MM.

Results: Compared with controls, the MM group had a significantly higher frequency of the A allele in BsmI site (8.7% vs 2.4%) and C allele in the TaqI site (10.5% vs 3.6%). These two alleles were closely associated with an increased risk of MM ($P = .025$; $P = .030$). The highly rare genotypes (BsmI-AA and TaqI-CC) were found in one patient with MM.

Conclusion: *VDR* gene polymorphisms may be a molecular marker of MM risk.

KEYWORDS

gene polymorphism, multiple myeloma, SNP, vitamin D receptor

1 | INTRODUCTION

Multiple myeloma (MM) is a malignant clonal plasma cell disease, which occurs commonly in elderly male and is hard to cure. Epidemiological data have shown that the incidence of MM accounts for about 10% of hematologic cancers, which is the second common among hematologic cancers, and 2% of all malignant cancers.[1,2] The average survival time of MM is 3 to 4 years and most patients end up with recurrence. The major symptoms of MM include osteolytic lesions, bone pain, pathological fractures, and hypercalcemia.[3-6] Traditionally, the mechanism of MM has been believed that myeloma cells secrete inhibitory factors, resulting in bone destruction and osteogenesis inhibition. Cytogenetic studies of MM suggest that the malignant transformation is the result of a multigene interaction with the environment. When exposed to similar environment factors, only a small number of individuals suffer from MM, suggesting a genetic susceptibility during MM development. Therefore, it is worth to probe the specific genetic polymorphism and its correlation with MM susceptibility and clinical prognosis. Single-nucleotide polymorphism (SNP) is an ideal method to study the driving cause of malignant cancers at the genetic level. It probes the polymorphism of DNA sequences caused by single nucleotide mutation at the whole genome level. Each SNP has 100 to 300 bp on average, and the cleavage reaction usually produces only 2 to 3 fragments, which provide limited information and are affected by variety of factors (eg, the purity of DNA samples). Direct sequencing is the most sensitive method for SNP and mutation site detection, which helps to observe the clear base sequence and directly reflects the relationship between genotype and phenotype.

The candidate genes in SNP research related to myeloma risk are mainly oncogenes (such as *c-myc*, *bcl-2*, and *K-ras*), tumor suppressor genes (like *p53* and *Rb1*), and cytokine receptor genes (*IL-6*, *IL-1B*, *IL- 8*, *TNF*, *TGF*, *G-CSF*, *EPO*, *HLA*, *MTHFR*, *MDR*, *Jak2*, and so on). Theoretically, vitamin D receptor (*VDR*) gene could influence clinical manifestations of bone disease in all possibility. However, there have been very few reports demonstrating the relationship between *VDR* and MM.[7,8] A novel study showed that the proteasome inhibitor bortezomib treatment on patients with MM increased the VDR signal pathway and thus stimulated osteogenic differentiation.[9] VD is a necessary lipid soluble vitamin, and also a steroid.[1,10] Studies have confirmed that VD interferes multiple signaling pathways (such as IGF, TGF-β, Wnt/β-catenin, and ERK) associated with cell growth, and other signaling pathways (β-catenin, c-Jun, PI3K, NF-κB, and c-myc) influencing cancer progression.[8,10-17] The pathways involved in the pathogenesis of MM can be modulated by the VDR signaling. For example, EB1089 (a novel 1,25-dihydroxyvitamin D3 analog) can block MM in NCIH929 cells and inhibit the cellular growth, when it activates p38 and inhibiting ERK and promoted apoptosis.[18] Given VDR is a critical way for series of biological effects, VDR polymorphisms are here highly possibly associated with the MM development and prognosis. VDR polymorphism may decide the expression of messenger RNA (mRNA) and consequently cause differences in the number or activity of the receptor protein, which finally affects the function of VDR by regulating the expression of hormone-sensitive-gene mediated VD3 effects. VDR is encoded by a large gene (>100 kb) located on chromosome 12cen-q12 containing 14 exons. Presently, known cleavage sites of the *VDR* gene associated with bone and calcium metabolism are FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236). The former three are most common SNPs in VDR gene polymorphism. The presence of these four sites are generally labeled f, b, a, and t, and lack of them are usually labeled F, B, A, and T (Figure 1A). This study focused on the mutation and polymorphic loci of the *VDR* gene in patients with MM, and our findings enrich the genetic and pathogenesis data of MM in Chinese population.

2 | MATERIALS AND METHODS

2.1 | Design and subjects

This study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University [(2014) No. 082]. All subjects had received an informed consent. From August 2014 to February 2016, we enrolled 40 cases of patients with MM, including 23 males and 17 females (aged 34-81 years, mean age 59.5). Besides, 84 cases of health controls with comparable ages

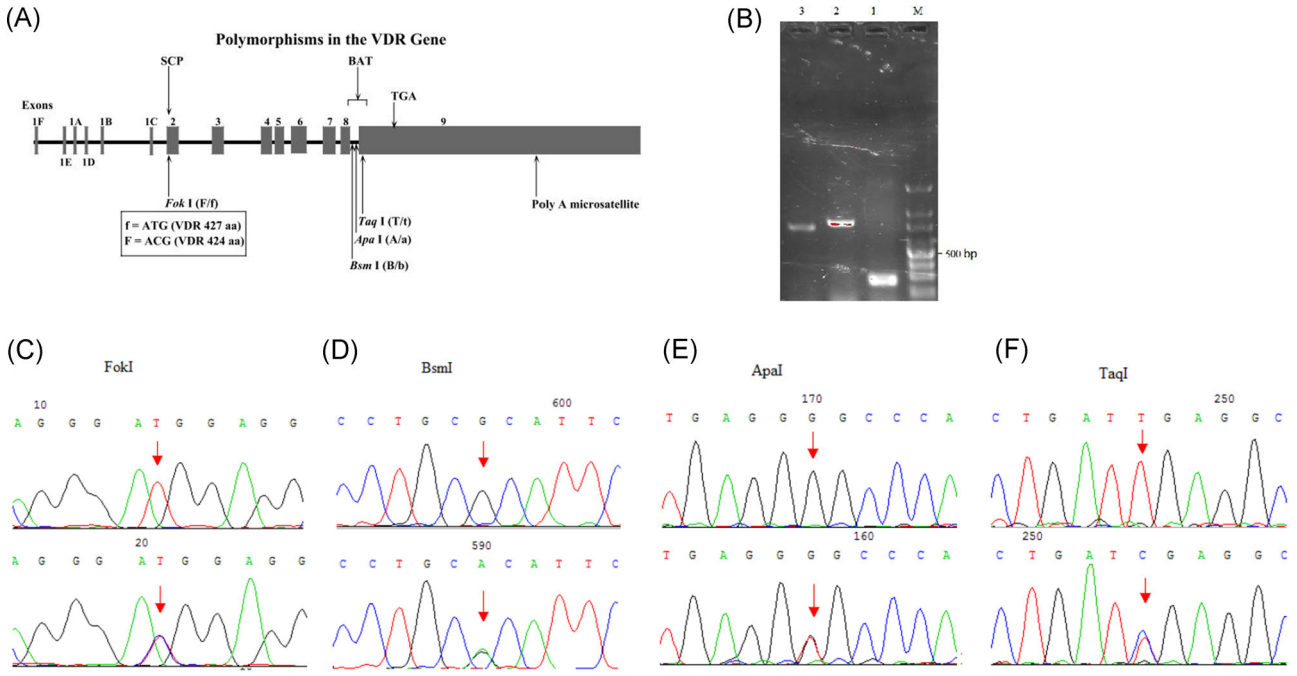

FIGURE 1 PCR product lengths and DNA sequencing of FokI, BsmI, and ApaI/TaqI polymorphisms. A, Four sites are labeled in the *VDR* gene. B, FokI, BsmI, and ApaI/TaqI have different product lengths (FokI 273 bp, BsmI 823 bp, and ApaI/TaqI 745 bp). C-F, Different polymorphisms of four sites from DNA sequencing results (C, FokI TT, TC, and CC types; D, BsmI GG, AG, and AA types; E, ApaI GG, TG, and TT types; F, TaqI TT, CT, and CC types). PCR, polymerase chain reaction

and sex ratio to the patients with MM were enrolled. All subjects had lived in the Fujian province for a long time, without any blood relationship. For each subject, we collected 5 mL of the fasting elbow vein blood in the morning. Under anticoagulation treatment (3.8% citrate sodium), samples were transferred into the −80°C refrigerator.

2.2 | DNA extraction and purity determination

Following the steps of the DNA extraction kit (Kangwei Biotechnology Co., Ltd. Beijing, China), DNA samples were purified from the blood. To determine the concentration, 2 μL of extracted DNA solution was carefully dropped into the UV spectrophotometer. When the OD260/280 ratio was between 1.8 and 2.0, the DNA purity was regarded as standard, and these samples were stored at −20°C.

2.3 | PCR amplification

The PCR reaction system contain 25 μL of mixture (volume μL): TaKaRa Ex Taq 0.125, 10 × Ex Taq buffer 2.5, dNTP mixture 2.0, template DNA 2.0, primer-F 0.8, Primer-R 0.8, and sterilized distilled water 16.775. The PCR reaction program was as follow: 94°C predenaturation for 5 minutes, 94°C denaturation for 30 seconds, 60.8 to 61.5°C annealing for 30 seconds (BsmI, Apa I, TaqI, and FokI at 61.5°C, 60.8°C, 60.8°C, and 61.5°C, respectively), 72°C extension for 60 seconds. A total of 30 cycles were performed and the PCR products were stored at 4°C. The primers for each site are listed in Table 1.

2.4 | Detection of PCR-amplification products

The amplification products were detected using 1.5% agarose-gel electrophoresis (with GoldenView nucleic acid dye). For each lane, 12 μL of mixture (products: loading buffer = 5:1) was added into the channel. The 100-bp DNA ladder markers were used as the molecular references. After 20 minutes of 100 V electrophoresis, the gel was transferred into the UV gel imaging analyzer to observe the electrophoresis band.

2.5 | DNA sequencing

The DNA amplification products were sent for sequencing by Boshang Biology Co., Ltd. The sequencing results were analyzed by CHROMAS program and compared with the GeneCards and NCBI databases using BLAST and Ensembl (reference sequence NG_008731.RefSeqGene), through which we ensured whether the discovered new sites were mutation or new SNPs.

2.6 | Statistical analysis

The genotype, allele, linkage disequilibrium (LD), and haplotype were analyzed by SHEsis online bioinformatics software (http://shesisplus.bio-x.cn/SHEsis.html) for the MM group and the control group, and the Hardy-Weinberg equilibrium, Odds ratio (OR) and 95% confidence interval (CI) were determined using χ^2 test or Fisher exact test (double tail). $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | PCR amplification and DNA sequencing

As Figure 1B shown, FokI, BsmI, and ApaI/TaqI had different product lengths (FokI 273 bp, BsmI 823 bp, and ApaI/TaqI 745 bp). Based on sequencing findings, three different genotypes of each site were presented in Figure 1C–F (Figure 1C: FokI TT, TC, and CC types; Figure 1D: BsmI GG, AG, and AA types; Figure 1E: ApaI GG, TG, and TT types; Figure 1F: TaqI TT, CT, and CC types).

TABLE 1 VDR polymorphism primers

SNP	Primer sequence	Products (bp)
FokI	5′-GATGCCAGCTGGCCCTGGCACTG-3′	273 bp
	5′-ATGGAAACACCTTGCTTCTTCTCCCTC-3′	
BsmI	5′-CAACCAAGACTACAAGTACCGCGTCAGTGA-3′	823 bp
	5′-AACCAGCGGAAGAGGTCAAGGG-3′	
ApaI/TaqI	5′-AGAGCATGGACAGGGAGCAAG-3′	745 bp
	5′-GCAACTCCTCATGGCTGAGGTCTCA-3′	

Abbreviations: SNP, single-nucleotide polymorphism; VDR, vitamin D receptor.

3.2 | Hardy-Weinberg genetic balance analysis

The *P* values of Hardy-Weinberg genetic balance for FokI, BsmI, ApaI, and TaqI analysis in the MM group and control group were respectively: 0.825212 and 0.106997, 0.169557 and 0.820912, 0.192173 and 0.770267, and 0.318723 and 0.734285. These data confirmed that the four sites of all subgroups were in accordance with the Hardy-Weinberg genetic balance and implied that samples were derived from random-marriage populations and could represent a general situation.

3.3 | The allele distribution frequency and MM susceptibility

The summarized analysis of the genotype and allele frequency in two groups are presented in Table 2. Among all the patients with MM, the wild type TT genotype of the FokI locus accounted for 20% (8 cases), the heterozygous polymorphism TC genotype accounted for 47.5% (19 cases), and the homozygous polymorphism CC genotype accounted for 32.5% (13 cases). For the BsmI locus, the wild type GG genotype accounted for 85% (34 cases), the GA genotype accounted for 12.5% (5 cases), and the AA genotype accounted for 2.5% (1 case). For the ApaI locus, the GG genotype of accounted for 31.6% (12 cases), the TG genotype accounted for 57.9% (22 cases), and the TT genotype accounted for 10.5% (4 cases). For TaqI locus, there were 81.6% (31 cases) TT genotype, 15.8% (6 cases) TC polymorphism genotype, and 2.6% CC genotype (1 case). The frequency of allele A distribution in the BsmI locus was significantly higher ($P = .025$) in the MM group (8.7%) than control (2.4%), and the AA genotype (2.5%) only appeared in the MM group, which suggests that allele A in the BsmI locus may be a

TABLE 2 Genotypes and allele frequency in two groups

Polymorphism	Characteristic	MM n = 40/38	Control n = 84	OR (95% CI)	χ^2	*P*
FokI	Genotypes					
	TT	8 (0.200)	8 (0.095)	–	2.658	.265
	CC	13 (0.325)	30 (0.357)			
	TC	19 (0.475)	46 (0.548)			
	Allele					
	T	35 (0.438)	62 (0.369)	0.752 (0.437-1.293)	1.066	.302
	C	45 (0.562)	106 (0.631)			
BsmI	Genotypes					
	GG	34 (0.850)	78 (0.951)	–	4.467	.107
	AA	1 (0.025)	0 (0.000)			
	GA	5 (0.125)	4 (0.049)			
	Allele					
	G	73 (0.912)	160 (0.976)	3.835 (1.089-13.513)	4.975	.025
	A	7 (0.087)	4 (0.024)			
ApaI	Genotypes					
	TT	4 (0.105)	8 (0.095)	–	3.762	.152
	GG	12 (0.316)	42 (0.500)		–	–
	TG	22 (0.579)	34 (0.405)			
	Allele					
	T	30 (0.395)	50 (0.298)	0.649 (0.368-1.144)	2.239	.134
	G	46 (0.605)	118 (0.702)			
TaqI	Genotypes					
	TT	31 (0.816)	78 (0.929)	–	4.572	.102
	CC	1 (0.026)	0 (0.000)			
	TC	6 (0.158)	6 (0.071)			
	Allele					
	T	68 (0.895)	162 (0.964)	3.176 (1.062-9.502)	4.679	.030
	C	8 (0.105)	6 (0.036)			

high-risk allele regarding to MM. Besides, the frequency of C allele within the TaqI locus in the MM group (10.5%) was significantly higher ($P = .03$) than the control group (3.6%), and similarly, the CC genotype (2.6%) only appeared in the MM group but never in the control group, which implies that allele C in the TaqI is positively associated with the MM development.

In addition, we found one MM case had two rare genotypes, BsmI AA genotype and TaqI CC genotype, respectively. As mentioned above, the A allele in BsmI site and the C allele in TaqI site are high-risk indicator of MM. The early diagnosis of this patient by bone marrow aspiration displayed that the myeloma cells accounted for 78%. Nine months after autologous peripheral blood stem cell transplantation and chemotherapy therapy (combination of bortezomib, adriamycin, and dexamethasone), this patient was found a MM recurrence.

4 | DISCUSSION

In this study, we explored the relationship between VDR and the incidence of MM from genotype, allele, and haplotype frequency distribution, and observed the distribution characteristics of VDR polymorphism in Fujian province. Our findings highlight that VDR polymorphism is closely associated with the MM development and progress.

VDR is widely located in almost all cells and can be divided into nuclear receptor and membrane receptor. The former affects gene expression and controls the protein synthesis, and the later majorly maintains calcium and phosphorus balance. VDR gene polymorphism has been known to influence the susceptibility to type 1 and 2 diabetes,[19-21] bone density in postmenopausal women,[15,22,23] AIDS disease progression,[24] spine bone mineral density,[25] and multiple types of cancers. Low-serum vitamin D is an important contributor to the skeletal complications, which can be the major causes of MM. To date, research works have mainly focused on the traditional roles of VD-VDR signaling, like calcium deposition and bone density. Very few studies have provided data about the VDR polymorphism in MM. In 2013, a study of Kashmiri population revealed that FokI polymorphism was involved in the increased susceptibility to MM development and progression.[8] Recently, another study pointed out that T allele of FokI within *VDR* gene was associated with an increased MM risk.[26] Besides, the VDR polymorphism FokI was associated with greater vitamin D3-dependent growth inhibition in myeloma cells.[26] These results partially support our conclusion that *VDR* gene polymorphisms may be a molecular marker of MM risk. However, we have not found the relationship between FokI polymorphism and MM, instead, BsmI and TaqI polymorphism were different between patients with MM and controls. This inconsistency may be due to the population differences.

In this study, the frequencies of the FokI genotypes and the alleles were not statistically different between the two groups, and they were not associated with the MM incidence rate. However, FokI was correlated with sex, and serum calcium in the MM group (data not shown). Lack of FokI, VD cannot influence the proliferation, differentiation, and apoptosis of VDR-deficient cells. Besides, when VDR is less sensitive to VD, the blood 1α, 25 (OH) 2D3 may increase, which further affects the PTH calcium and phosphorus regulation. Shafia et al. confirm that the FokI locus is associated with MM susceptibility, and the ff genotype is associated with creatinine levels as a risk factor of disease progression; moreover, the ff genotype is also associated with low levels of VD.[8] This report is consistent with our additional findings. The A allele at the BsmI site is a high-risk allele for MM. Although we have not discovered statistically significant differences among genotypes, it is noteworthy that some studies have shown that the b allele is more active than the B allele.[27] Furthermore, BB genotype is associated with higher 1α, 25 (OH) 2D3 expression than the bb/Bb genotype.[28] The frequency distribution of the genotypes and alleles of the ApaI locus were found neither statistically different between two groups nor associated with the risk of MM. However, the ApaI locus was found to be related to the age of onset in the case group (not shown). Finally, C allele in the TaqI locus is a high-risk allele of MM. TaqI site may affect the balance between TH1 and TH2. The tt homozygous type promotes the TH1 immune response and the TT type triggers the TH2 type immune response. Besides. the TT genotype is associated with a low-cycling activity of VD3.[29] Our findings are consistent with a new meta-analysis, which identified 126 VDR polymorphisms and found that the FokI locus f allele is a high-risk allele for ovarian cancer and skin cancer. The BsmI site was significantly associated with cancer risk (skin cancer and colorectal cancer) in the Caucasian population. However, the B allele was considered a protective factor for melanoma. The alleles in the ApaI locus were thought to influence the susceptibility to basal cell carcinoma in the Asian population. The TaqI locus could decide the onset of oral and breast cancer, as well as basal cell carcinoma.[30] As far as we discovered, none of FokI, ApaI BsmI, and TaqI locus could be considered independent prognostic factors of MM, besides factors such as sun exposure, outdoor activity, VD levels, calcium Intake, obesity, smoking, etc.

In conclusion, the frequencies of A allele in BsmI or C allele in the TaqI polymorphisms are increased in the

patients with MM. These two alleles are closely associated with an increased risk of MM. *VDR* gene polymorphisms may be a molecular marker for potential risk assessment in MM.

CONFLICTS OF INTEREST

The authors declare that there are no conflict of interests.

FUNDING

This study was supported by The Leading Project Funds of The Science and Technology Office of Fujian Province (2015Y0013).

ORCID

Hongbing Rui http://orcid.org/0000-0002-5948-8595

REFERENCES

1. Aggarwal R, Ghobrial IM, Roodman GD. Chemokines in multiple myeloma. *Exp Hematol*. 2006;34(10):1289-1295.
2. Pellegrino A, Ria R, Di Pietro G, et al. Bone marrow endothelial cells in multiple myeloma secrete CXC-chemokines that mediate interactions with plasma cells. *Br J Haematol*. 2005;129(2):248-256.
3. Ramsenthaler C, Kane P, Gao W, et al. Prevalence of symptoms in patients with multiple myeloma: a systematic review and meta-analysis. *Eur J Haematol*. 2016;97(5):416-429.
4. Vickrey E. Multiple myeloma: vague symptoms can challenge diagnostic skills. *JAAPA*. 2008;21(11):19-22.
5. Zhang XY, Jiang YK, Xu B, Hu YK, Xue YL, Jiang WM. Establishment and characterization of six novel hepatocellular carcinoma cell lines from Chinese patient-derived tumor xenografts. *Int J Clin Exp Pathol*. 2017;10(3):3033-3042. 2017
6. Catamero D, Noonan K, Richards T, et al. Distress, fatigue, and sexuality: understanding and treating concerns and symptoms in patients with multiple myeloma. *Clin J Oncol Nurs*. 2017;21(5):7-18.
7. Liu Y, Rui HB. Mutations of vitamin D receptor gene found in patients with multiple myeloma. *Zhonghua Zhong Liu Za Zhi*. 2017;39(2):121-126.
8. Shafia S, Qasim I, Aziz SA, Bhat IA, Nisar S, Shah ZA. Role of vitamin D receptor (VDR) polymorphisms in susceptibility to multiple myeloma in ethnic Kashmiri population. *Blood Cells Mol Dis*. 2013;51(1):56-60.
9. Kaiser MF, Heider U, Mieth M, Zang C, von Metzler I, Sezer O. The proteasome inhibitor bortezomib stimulates osteoblastic differentiation of human osteoblast precursors via upregulation of vitamin D receptor signalling. *Eur J Haematol*. 2013;90(4):263-272.
10. Horie-Inoue K, Inoue S. Steroid and xenobiotic receptor mediates a novel vitamin K2 signaling pathway in osteoblastic cells. *J Bone Miner Metab*. 2008;26(1):9-12.
11. Gilad LA, Bresler T, Gnainsky J, Smirnoff P, Schwartz B. Regulation of vitamin D receptor expression via estrogen-induced activation of the ERK 1/2 signaling pathway in colon and breast cancer cells. *J Endocrinol*. 2005;185(3):577-592.
12. Shen Q, Christakos S. The vitamin D receptor, Runx2, and the Notch signaling pathway cooperate in the transcriptional regulation of osteopontin. *J Biol Chem*. 2005;280(49):40589-40598.
13. Wen Y, Da M, Zhang Y, et al. Alterations in vitamin D signaling pathway in gastric cancer progression: a study of vitamin D receptor expression in human normal, premalignant, and malignant gastric tissue. *Int J Clin Exp Pathol*. 2015;8(10):13176-13184.
14. Chen L, Khillan JS. A novel signaling by vitamin A/retinol promotes self renewal of mouse embryonic stem cells by activating PI3K/Akt signaling pathway via insulin-like growth factor-1 receptor. *Stem Cells*. 2010;28(1):57-63.
15. Xu H, Xiong DH, Xu FH, Zhang YY, Lei SF, Deng HW. Association between VDR ApaI polymorphism and hip bone mineral density can be modified by body mass index: a study on postmenopausal Chinese women. *Acta Biochim Biophys Sin (Shanghai)*. 2005;37(1):61-67.
16. Daniel C, Schroder O, Zahn N, Gaschott T, Stein J. p38 MAPK signaling pathway is involved in butyrate-induced vitamin D receptor expression. *Biochem Biophys Res Commun*. 2004;324(4):1220-1226.
17. Peehl DM, D. Feldman: Interaction of nuclear receptor ligands with the Vitamin D signaling pathway in prostate cancer. *J Steroid Biochem Mol Biol*. 2004;92(4):307-315.
18. Kumagai T, O'Kelly J, Said JW, Koeffler HP. Vitamin D2 analog 19-nor-1,25-dihydroxyvitamin D2: antitumor activity against leukemia, myeloma, and colon cancer cells. *J Natl Cancer Inst*. 2003;95(12):896-905.
19. Lopez T, García D, Angel B, et al. Association between Fok I vitamin D receptor (VDR) gene polymorphism and plasmatic concentrations of transforming growth factor-beta1 and interferon gamma in type 1 diabetes mellitus. *Med Clin (Barc)*. 2008;130(3):81-84.
20. Audi L, Martí G, Esteban C, et al. VDR gene polymorphism at exon 2 start codon (FokI) may have influenced Type 1 diabetes mellitus susceptibility in two Spanish populations. *Diabet Med*. 2004;21(4):393-394.
21. Boucher BJ. Association between vitamin D receptor (VDR) polymorphism and type 2 diabetes. *Metabolism*. 2002;51(10):1375-1375. author reply 1375
22. Moffett SP, Zmuda JM, Cauley JA, et al. Association of the VDR translation start site polymorphism and fracture risk in older women. *J Bone Miner Res*. 2007;22(5):730-736.
23. Brodowska A. The influence of hormonal replacement therapy on bone density in postmenopausal women depending on polymorphism of vitamin D receptor (VDR) and estrogen receptor (ER) genes. *Ann Acad Med Stetin*. 2003;49:111-130.
24. Nieto G, Barber Y, Rubio MC, Rubio M, Fibla J. Association between AIDS disease progression rates and the Fok-I polymorphism of the VDR gene in a cohort of HIV-1 seropositive patients. *J Steroid Biochem Mol Biol*. 2004;89-90(1-5):199-207.
25. Pluskiewicz W, Zdrzalek J, Karasek D. Spine bone mineral density and VDR polymorphism in subjects with ulcerative colitis. *J Bone Miner Metab*. 2009;27(5):567-573.
26. Gascoyne DM, Lyne L, Spearman H, Buffa FM, Soilleux EJ, Banham AH. Vitamin D receptor expression in plasmablastic

lymphoma and myeloma cells confers susceptibility to vitamin D. *Endocrinology*. 2017;158(3):503-515.

27. Whitfield GK, Remus LS, Jurutka PW, et al. Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene. *Mol Cell Endocrinol*. 2001;177(1-2):145-159.
28. Morrison NA, Qi JC, Tokita A, et al. Prediction of bone density from vitamin D receptor alleles. *Nature*. 1994;367(6460):284-287.
29. Ma J, Stampfer MJ, Gann PH, et al. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. *Cancer Epidemiol Biomarkers Prev*. 1998;7(5):385-390.
30. Xu Y, He B, Pan Y, et al. Systematic review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. *Tumour Biol*. 2014;35(5):4153-4169.

How to cite this article: Rui H, Liu Y, Lin M, Zheng X. Vitamin D receptor gene polymorphism is associated with multiple myeloma. *J Cell Biochem*. 2019;1-7. https://doi.org/10.1002/jcb.29135