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ORIGINAL ARTICLE

Genetic variation in the maternal vitamin D receptor FokI gene as a risk factor for recurrent pregnancy loss

Anita Barišić[a], Nina Pereza[a], Alenka Hodžić[b], Milena Gašparović Krpina[c], Saša Ostojić[a] and Borut Peterlin[b]

[a]Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia; [b]Clinical Institute of Medical Genetics, UMC, Ljubljana, Slovenia; [c]Department of Obstetrics and Gynecology, Clinical Hospital Center "Rijeka", Rijeka, Croatia

ABSTRACT

Purpose: Recurrent pregnancy loss (RPL) is a reproductive disorder defined as the loss of two or more pregnancies before 24 weeks of gestation. Despite the fact that several mechanisms have been previously described for the pathogenesis of RPL, the causes of ~50% of cases remain unknown. However, recent studies indicate association of vitamin D deficiency with adverse pregnancy outcome, including RPL. The vitamin D receptor (VDR) is a crucial mediator of the pleiotropic cellular effects of vitamin D. Its function is influenced by several single nucleotide polymorphisms (SNPs). The main objective of this study is to assess whether maternal VDR SNPs are associated with the risk of RPL in Slovenian and Croatian women.

Methods: A case–control study including 320 women with RPL and control women is designed to examine the potential association of VDR polymorphisms (FokI rs222857, Cdx2 rs11568820, and Taq1 rs731236) with RPL. Genotyping is performed using polymerase chain reaction and restriction fragment length polymorphism methods.

Results: We find a statistically significant higher frequency of the rs222857 CC genotype ($\chi^2 = 6.61$, $p = .036$) and C allele ($\chi^2 = 5.93$, $p = .015$) in RPL women compared to controls. Subsequently, the odds for RPL for the rs222857 are increased under the recessive (CCvsCT + TT: OR = 1.78; 95% CI = 1.12–2.82; $p = .015$) and the codominant (CCvsTT: OR = 2.21; 95% CI = 1.08–4.53; $p = .029$; CCvsCT: OR = 1.68; 95% CI = 1.04–2.72; $p = .036$) genetic models. The other two analyzed polymorphisms did not show any statistical significant result.

Conclusions: Our results suggest that variations in the maternal VDR FokI gene might be associated with RPL in Slovenian and Croatian women.

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Pregnancy; recurrent pregnancy loss; single nucleotide polymorphism; vitamin D receptor

Introduction

Recurrent pregnancy loss (RPL) is a reproductive disorder defined as the loss of two or more pregnancies from the time of conception until 24 weeks of gestation [1]. Although the exact prevalence of RPL is difficult to estimate, it ranges from 2 to 3% when taking into the account clinical miscarriages and biochemical losses. Therefore, it is considered as a common pregnancy complication that has a significant psychological impact on women and their partners. Despite the fact that several mechanisms have been previously described for the pathogenesis of RPL, including fetal and/or parental chromosomal anomalies, uterine abnormalities, infections, endocrine, and autoimmune disorders, the causes of ~50% of RPL still remain unknown [2,3].

The active form of vitamin D, 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), is a lipid-soluble hormone that plays a vital role in calcium homeostasis and skeletal metabolism [4]. In addition to these functions, vitamin D modulates the immune system and cell proliferation [5]. Moreover, recent studies indicate association of vitamin D deficiency with infertility, polycystic ovary syndrome, *in vitro* fertilization outcomes and male gonadal function [6,7]. Besides, vitamin D and its components may have a significant influence on feto-placental development and expression of multiple placental hormones (human chorionic gonadotropin, human placental lactogen, estradiol, progesterone) and proinflammatory cytokines [8–11]. Furthermore, a high proportion of RPL patients have vitamin D deficiency, and low concentrations of vitamin D have

CONTACT Nina Pereza nina.pereza@medri.uniri.hr Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, B. Branchetta 20, Rijeka, Croatia

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been associated with an increased risk of first trimester miscarriage [12,13].

The vitamin D receptor (VDR) is a crucial mediator of the pleiotropic cellular effects of vitamin D. Expression and nuclear activation of the VDR is indispensable for the effects of vitamin D. The VDR is a ligand-activated transcription factor identified in a variety of cells and tissues. It modulates the transcription of target genes in response to $1,25(OH)_2D_3$ binding [6,7]. The gene encoding VDR is located on the chromosome 12. Although 470 common single nucleotide polymorphisms (SNPs) have been identified in the VDR gene, in the Caucasian population several common allelic variants have been extensively studied in relation to the risk of developing diseases. We chose FokI rs222857, Cdx2 rs11568820, Taq1 rs731236 SNPs based on their previous association with susceptibility to a range of diseases, including gynecological and nongynecological cancers, as well as medical disorders connected with pregnancy pathologies and the ones which are not associated with pregnancy at all [14–20]. However, association of these SNPs with RPL has not been previously investigated.

Accordingly, the aim of this study was to evaluate whether three different maternal VDR SNPs Cdx2 rs11568820, FokI rs22285, and Taq1 rs731236 are associated with the risk of RPL in Slovenian and Croatian women.

Materials and methods

Patients

A case–control study including 320 women with RPL and control women (298 Slovenian and 22 Croatian) was designed to examine the potential association of VDR polymorphisms (FokI rs222857, Cdx2 rs11568820, and Taq1 rs731236) with RPL. Samples were collected at the Clinical Institute of Medical Genetics, UMC, Ljubljana, Slovenia, and Department of Obstetrics and Gynaecology, Clinical Hospital Centre of Rijeka, Croatia. Samples collected in Rijeka are part of the TransMedri biobank—Bank of biosamples for the investigation of spontaneous and medically induced abortions (EU-FP7 Regpot-2010-5, Faculty of Medicine, University of Rijeka). Each participant signed a written and informed consent before enrolment. The study was approved by Slovenian and Croatian Ethics' Committees.

Participants were divided into two groups. The RPL group involved 160 women with a history of 3 or more consecutive miscarriages from the time of conception until 24 weeks of gestation, the etiology of which could not be explained by other risk factors included in the conventional RPL evaluation. Exclusion criteria were: abnormal parental karyotypes, women with uterine anatomic abnormalities, endocrine or metabolic disorders, autoimmune diseases or other systemic disorders including antiphospholipid syndrome, and previous venous or arterial thrombosis. A total of 106 (66.3%) of women had no live births (primary RPL), whereas 54 (33.7%) had at least one live-born child (secondary RPL). Characteristics of RPL women (parity, number of spontaneous abortions, gestational age) are presented in the Supplementary Table 1. The control group involved 160 unrelated, healthy women with a history of at least two normal term deliveries and no record of spontaneous abortion or any other reproductive disorder.

Molecular and general genetics methods

Genomic DNA was extracted from peripheral blood leukocytes by standard procedures using a commercially available kit (QiagenFlexiGene DNA kit, Qiagen, Hilden, Germany). Extracted DNA was stored at –20 °C until further use.

The VDR polymorphisms (FokI rs222857, Cdx2 rs11568820, and Taq1 rs731236) were determined using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) methods. Polymerase chain reaction was carried in thermal cyclers (Mastercycle Personal, Eppendorf, Hamburg, Germany and 2720 Thermal Cycler, Applied Biosystems, Carlsbad, CA, USA). The restriction digested PCR products were loaded and separated into 3% agarose gels containing GelRed (Olerup SSP, Saltsjobaden, Sweden). The presence of specific genotypes was determined by the band of expected size. For quality control, randomly selected PCR products were subjected to repeated genotyping to verify the results. The concordance was 100%.

Supplementary Table 2 summarizes primer sequences for each studied SNP, restriction enzymes used in the study, and expected sizes of restriction products.

Statistical analysis

All data were analyzed using Statistica, version 13.3.0 (TIBCO Software Inc, Palo Alto, CA, USA). Statistical power and sample size were calculated using DSS Researcher's Toolkit (www.dssresearch.com/toolkit/spcalc/power_p2.asp). The statistical power of the study was 93% to detect a 1.5-fold increase in the frequency of the FokI rs222857 T allele, 91% to detect a

1.8-fold increase in the frequency of the Cdx2 rs11568820 A allele, and 93% to detect a 1.5-fold increase in the frequency of the Taq1 rs731236 T allele.

The allele and genotype frequencies obtained in our population are displayed with the frequency of the control group. They are consistent with Central European population frequencies (https://www.ncbi.nlm.nih.gov/snp/). Hardy–Weinberg analysis was performed to compare the observed and expected genotype frequencies using Simple Hardy–Weinberg Calculator-Court Lab (Washington State University College of Veterinary Medicine, Pullman, WA, USA). The results did not deviate from Hardy–Weinberg equilibrium in any of the study groups (data not shown).

Differences in allele and genotype frequencies between patients and controls were determined using standard Chi-square test. The odds ratio (OR) and associated 95% confidence intervals (95% CI) were calculated to estimate associations of FokI rs222857, Cdx2 rs11568820, and Taq1 rs731236 genotypes and alleles with RPL (MedCalc for Windows, version 14.12.0, MedCalc Software, Mariakerke, Belgium). The data were analyzed under recessive, dominant, and codominant inheritance models.

All tests applied were two-tailed and a p value $\leq .05$ was regarded statistically significant.

Results

We found a statistically significant higher frequency of the FokI rs222857 CC genotype ($\chi^2 = 6.61$, $p = .036$) and C allele ($\chi^2 = 5.93$, $p = .015$) in women with RPL compared to controls (Table 1). Additionally, the odds for RPL in women were increased under the recessive (CCvsCT + TT: OR = 1.78; 95% CI = 1.12–2.82; $p = .015$) and codominant genetic models (CCvsTT: OR = 2.21; 95% CI = 1.08–4.53; $p = .029$; CCvsCT: OR = 1.68; 95% CI = 1.04–2.72; $p = .036$) (Table 2). Taq1 rs731236 C allele showed a statistically significant higher frequency in women with RPL compared to controls ($\chi^2 = 4.13$, $p = .042$; OR = 1.39; 95% CI = 1.01–1.92; $p = .042$) (Tables 1 and 2).

However, the genotype and allele frequencies of Cdx2 rs11568820 did not differ significantly between patient and control groups (Table 1). Moreover, there was no statistically significant association between the Cdx2 rs11568820 genotypes and alleles and the risk of RPL under any genetic model (Table 2).

Table 1. Genotype and allele frequencies of FokI rs222857, Cdx2 rs11568820, and Taq1 rs731236 gene polymorphisms in women with RPL and control women.

	Patients *n* (%)	Controls *n* (%)	χ^2	*p* value
FokI rs222857				
Genotype			6.61	.036
CC	68 (42.5)	47 (29.4)		
CT	75 (46.9)	87 (54.4)		
TT	17 (10.6)	26 (16.2)		
Allele			5.93	.015
C	211 (65.9)	181 (56.6)		
T	109 (34.1)	139 (43.4)		
Cdx2 rs11568820				
Genotype			0.74	.689
GG	111 (69.4)	112 (70.0)		
AG	41 (25.6)	43 (26.9)		
AA	8 (5.0)	5 (3.1)		
Allele			0.18	.675
G	263 (82.2)	267 (83.4)		
A	57 (17.8)	53 (16.6)		
Taq1 rs731236				
Genotype			3.68	.159
CC	73 (45.6)	59 (36.9)		
CT	64 (40.0)	67 (41.9)		
TT	23 (14.4)	34 (21.2)		
Allele			4.13	.042
C	210 (65.6)	185 (57.8)		
T	110 (34.4)	135 (42.2)		

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of RPL in women according to different genetic models.

		RPL versus controls	
SNP and model		OR (95% CI)	*p* Value
Fok1 rs222857			
Dominant	CC + CT vs. TT	1.63 (0.85–3.14)	.143
Recessive	CC versus CT + TT	1.78 (1.12–2.82)	.015
Codominant	CC versus TT	2.21 (1.08–4.53)	.029
	CC versus CT	1.68 (1.04–2.72)	.036
	TT versus CT	0.76 (0.38–1.51)	.429
Allele	C versus T	1.49 (1.08–2.05)	.015
Cdx2 rs11568820			
Dominant	GG + AG vs. AA	0.61 (0.19–1.92)	.399
Recessive	GG versus AG + AA	0.97 (0.60–1.56)	.903
Codominant	GG versus AA	0.62 (0.19–1.95)	.413
	GG versus AG	1.04 (0.63–1.72)	.880
	AA versus AG	1.68 (0.51–5.55)	.397
Allele	A versus G	1.09 (0.72–1.64)	.675
Taq1 rs731236			
Dominant	CC + CT vs. TT	1.61 (0.89–2.88)	.109
Recessive	CC versus CT + TT	1.44 (0.92–2.25)	.112
Codominant	CC versus TT	1.83 (0.97–3.44)	.061
	CC versus CT	1.29 (0.79–2.10)	.296
	TT versus CT	0.71 (0.38–1.33)	.283
Allele	C versus T	1.39 (1.01–1.92)	.042

The distribution of the FokI rs222857, Cdx2 rs11568820, and Taq1 rs731236 genotypes and allele frequencies in RPL and control groups, along with relevant statistical parameters for comparison are shown in Table 1. The associations between individual VDR polymorphisms and the risk of RPL in three genetic models (dominant, recessive, and codominant) are presented in Table 2.

Discussion

We found a statistically significant higher frequency of the FokI rs222857 CC genotype and C allele in RPL women compared to controls. Furthermore, the odds for RPL for the FokI rs222857 were increased under the recessive (CCvsCT + TT) and the codominant (CCvsTT; CCvsCT) genetic models. To the best of our knowledge, this is the first study investigating the association between the three VDR SNPs: FokI rs222857, Cdx2 rs11568820, Taq1 rs731236 and RPL.

Among the VDR polymorphisms, the FokI SNP is the only one that results in a VDR protein with a different structure. Moreover, it is the only polymorphism that is not in a linkage to any other VDR polymorphism, thus having an independent role [21]. The polymorphism is localized within the 5′ end of the gene and consists of a T to C Change. This change results in a protein with a different size: 424 amino acid (aa) variant, encoded by the major allele form (ACG) and a 427-aa variant, encoded by the minor allele form (ATG). These differences are considered to be functionally significant: the 424 aa VDR variant has more transcriptional activity and is connected with lower circulating 25(OH) D levels compared to the 427-aa variant [22,23]. Recent studies reported that serum 25(OH) D concentrations are lower in women with RPL, suggesting that low concentrations of 25(OH) D might be associated with RPL [24,25]. Moreover, Yan et al. [26] showed that women with RPL have lower levels of VDR expression in chorionic villi, decidua, and serum compared with normal pregnant women. These findings support our results, which suggest that CC genotype/424 aa VDR variant has a higher frequency in the women with RPL, that leads to lower circulating 25(OH) D levels, respectively.

Contrary to RPL, the potential role of FokI variant in the pathogenesis of other diseases is well known. It has been associated with different types of cancers, obesity, diabetes, autoimmune diseases [23,27–30]. Data from these studies seem to be contradictory to the results of our study by identifying the 427-aa variant as a hazardous one while we established the same one as a protective variant for RPL. Interestingly, the study by Van Etten et al. [21] reported that the lymphocytes, monocytes, and dendritic cells with a CC genotype/424 aa VDR variant, proliferate more strongly and express higher levels of IL-12 compared with those of an TT genotype/427 aa VDR variant, which might suggest the link between the immunological role of the FokI variant and the pathogenesis of RPL, a pregnancy complication well known for altered anti-inflammatory responses at the feto-placental unit [1].

Although the C allele of the TaqI SNP showed a statistically significant higher frequency in women with RPL compared to controls, a larger sample might be needed for conclusions on its association with RPL, giving the possibility of being associated with RPL. TaqI polymorphism is located at the 3′ untranslated region of VDR gene, which is involved in the regulation of gene expression, particularly through the modulation of mRNA stability. Precisely, the presence of TaqI G allele provides better VDR mRNA stability and half-life resulting with the increased VDR synthesis, thus directly affecting vitamin D levels and thereby subsequent effects of vitamin D [31,32]. Several studies reported on an association between this polymorphism and various diseases, including oral squamous cell carcinoma, severe diabetic retinopathy, urolithiasis, osteoarthritis [33–36].

The G to A polymorphism, located in a Cdx2 binding site in the 1e promoter region, is suggested to play an important role in intestinal transcription of the VDR gene. As the intestine is the main area for calcium absorption, the Cdx2 site is thought to control the vitamin D regulation of calcium absorption. The A allele has been demonstrated to be more effective than G allele by firmer binding the CDx2 transcription factor and expressing more transcriptional activity. Thus, the A allele is thought to cause increased VDR expression in the intestine, and thereby increased transcription of calcium transport proteins that will result with higher serum 25(OH) D level [37,38].

Despite the association of the spontaneous abortions with calcium levels an association between this SNP and RPL in Croatian and Slovenian women was not found.

Our study has a number of strengths related to study design that can reinforce the conclusions. The selection criteria for patients and controls were strict and based on new ESHRE evidence-based guidelines [1]. Both groups (patients and controls) comprised women who were similar for maternal age, ethnic background, area of residence, antenatal care, limiting the influence of known confounders. Statistical power for genotype and allele frequencies of observed gene polymorphisms and the associations between individual VDR polymorphisms and the risk of RPL in three genetic models was sufficient. The major limitation of this study, nonetheless, is a relatively small sample size and no data on vitamin D status and vitamin D supplement intake for the two cohorts.

Conclusions

Observed associations should be repeated in a larger cohort, as well as in other populations, taking into account that VDR is ethnicity dependent. Moreover, expression studies are needed to fulfil the understanding of the role of FokI polymorphisms in RPL etiology. Finally, the studies that can detect whether nutritional therapeutics can give a possible answer for the genetic preside position should also be provided. Since vitamin D levels can be altered through nutrition, it opens the way to new studies regarding the possible therapeutic route to affect the pregnancy outcome.

In conclusion, our results suggest that variations in the maternal VDR FokI gene might be associated with RPL in Slovenian and Croatian women.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] ESHRE Early Pregnancy Guideline Development Group. Recurrent pregnancy loss: guideline of the European Society of Human Reproduction and Embryology. 1st ed. Grimbergen (Belgium): European Society of Human Reproduction and Embryology; 2017. p. 15–18.

[2] Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Rev Obstet Gynecol. 2009;2(2):76–83.

[3] Toth B, Jeschke U, Rogenhofer N, et al. Recurrent miscarriage: current concepts in diagnosis and treatment. J Reprod Immunol. 2010;85(1):25–32.

[4] Tamblyn JA, Hewison M, Wagner CL, et al. Immunological role of vitamin D at the maternal-fetal interface. J Endocrinol. 2015;224(3):R107–R121.

[5] Lagishetty V, Liu NQ, Hewison M. Vitamin D metabolism and innate immunity. Mol Cell Endocrinol. 2011; 347(1–2):97–105.

[6] Shahrokhi SZ, Ghaffari F, Kazerouni F. Role of vitamin D in female reproduction. Clin Chim Acta. 2016;455: 33–38.

[7] Karras S, Anagnostis P, Kotsa K, et al. Vitamin D and gonadal function in men: a potential inverse U-shaped association? Andrology. 2016;4(3):542–544.

[8] Evans KN, Bulmer JN, Kilby MD, et al. Vitamin D and placental-decidual function. J Soc Gynecol Investig. 2004;11(5):263–271.

[9] Viganò P, Mangioni S, Pompei F, et al. Maternal-conceptus cross talk—a review. Placenta. 2003; 24(Suppl B):S56–S61.

[10] Piccinni MP, Scaletti C, Maggi E, et al. Role of hormone-controlled Th1- and Th2-type cytokines in successful pregnancy. J Neuroimmunol. 2000;109(1): 30–33.

[11] Murthi P, Yong HE, Ngyuen TP, et al. Role of the placental vitamin D receptor in modulating feto-placental growth in fetal growth restriction and pre-eclampsia-affected pregnancies. Front Physiol. 2016;7: 43.

[12] Ota K, Dambaeva S, Han AR, et al. Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Hum Reprod. 2014;29(2):208–219.

[13] Andersen LB, Jørgensen JS, Jensen TK, et al. Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage in the Odense Child Cohort. Am J Clin Nutr. 2015;102(3):633–638.

[14] Santoro D, Gagliostro G, Alibrandi A, et al. Vitamin D receptor gene polymorphism and left ventricular hypertrophy in chronic kidney disease. Nutrients. 2014;6(3):1029–1037.

[15] Rojano-Mejía D, Coral-Vázquez RM, Coronel A, et al. Relation of the estrogen receptor and vitamin D receptor polymorphisms with bone mineral density in postmenopausal Mexican-mestizo women. Gene. 2014;537(1):10–14.

[16] Shan JL, Dai N, Yang XQ, et al. FokI polymorphism in vitamin D receptor gene and risk of breast cancer among Caucasian women. Tumour Biol. 2014;35(4): 3503–3508.

[17] Vasilopoulos Y, Sarafidou T, Kotsa K, et al. VDR TaqI is associated with obesity in the Greek population. Gene. 2013;512(2):237–239.

[18] Aslani S, Hossein-Nezhad A, Mirzaei K, et al. VDR FokI polymorphism and its potential role in the pathogenesis of gestational diabetes mellitus and its complications. Gynecol Endocrinol. 2011;27(12):1055–1060.

[19] Fang X, Li H, Diao Y, et al. Polymorphisms in the MTHRF, VDR, MMP-9 and IL-β genes and the risk of premature rupture of membranes. Gynecol Obstet Invest. 2010;70(3):206–214.

[20] Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta. 2006; 371(1–2):1–12.
[21] Van Etten E, Verlinden L, Giulietti A, et al. The vitamin D receptor gene FokI polymorphism: functional impact on the immune system. Eur J Immunol. 2007; 37(2):395–405.
[22] Gombart F. Vitamin D: oxidative stress, immunity, and aging. Boca Raton: CRC Press; 2016. p. 248.
[23] Huang SP, Huang CY, Wu WJ, et al. Association of vitamin D receptor FokI polymorphism with prostate cancer risk, clinicopathological features and recurrence of prostate specific antigen after radical prostatectomy. Int J Cancer. 2006;119(8):1902–1907.
[24] Hou W, Yan XT, Bai CM, et al. Decreased serum vitamin D levels in early spontaneous pregnancy loss. Eur J Clin Nutr. 2016;70(9):1004–1008.
[25] Li N, Wu HM, Hang F, et al. Women with recurrent spontaneous abortion have decreased 25(OH) vitamin D and VDR at the fetal-maternal interface. Braz J Med Biol Res. 2017;50(11):e6527.
[26] Yan X, Wang L, Yan C, et al. Decreased expression of the vitamin D receptor in women with recurrent pregnancy loss. Arch Biochem Biophys. 2016;606: 128–133.
[27] Zhang K, Song L. Association between vitamin D receptor gene polymorphisms and breast cancer risk: a meta-analysis of 39 studies. PLoS ONE. 2014;9(4): e96125.
[28] Mittal RD, Manchanda PK, Bhat S, et al. Association of vitamin-D receptor (Fok-I) gene polymorphism with bladder cancer in an Indian population. BJU Int. 2007; 99(4):933–937.
[29] Mostowska A, Lianeri M, Wudarski M, et al. Vitamin D receptor gene BsmI, FokI, ApaI and TaqI polymorphisms and the risk of systemic lupus erythematosus. Mol Biol Rep. 2013;40(2):803–810.
[30] Angel B, Lera L, Sánchez H, et al. FokI polymorphism in vitamin D receptor gene: differential expression of TNFα in peripheral mononuclear cells of type 2 diabetic subjects. Meta Gene. 2016;7:1–6.
[31] Rosenfeld T, Salem H, Altarescu G, et al. Maternal-fetal vitamin D receptor polymorphisms significantly associated with preterm birth. Arch Gynecol Obstet. 2017; 296(2):215–222.
[32] Al-Daghri NM, Mohammed AK, Al-Attas OS, et al. Vitamin D receptor gene polymorphisms modify cardiometabolic response to vitamin D supplementation in T2DM patients. Sci Rep. 2017;7(1):8280.
[33] Taverna MJ, Sola A, Guyot-Argenton C, et al. Taq I polymorphism of the vitamin D receptor and risk of severe diabetic retinopathy. Diabetologia. 2002;45(3): 436–442.
[34] Bektas-Kayhan K, Unür M, Yaylim-Eraltan I, et al. Association of vitamin D receptor Taq I polymorphism and susceptibility to oral squamous cell carcinoma. In Vivo. 2010;24(5):755–759.
[35] Seyhan S, Yavascaoglu I, Kilicarslan H, et al. Association of vitamin D receptor gene Taq I polymorphism with recurrent urolithiasis in children. Int J Urol. 2007;14(12):1060–1062.
[36] Keen RW, Hart DJ, Lanchbury JS, et al. Association of early osteoarthritis of the knee with a Taq I polymorphism of the vitamin D receptor gene. Arthritis Rheum. 1997;40(8):1444–1449.
[37] Arai H, Miyamoto KI, Yoshida M, et al. The polymorphism in the caudal-related homeodomain protein Cdx-2 binding element in the human vitamin D receptor gene. J Bone Miner Res. 2001;16(7): 1256–1264.
[38] Pulito C, Terrenato I, Di Benedetto A, et al. Cdx2 polymorphism affects the activities of vitamin D receptor in human breast cancer cell lines and human breast carcinomas. PLoS ONE. 2015;10(4):e0124894.