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Original Article

Association of insulin-like growth factor I gene polymorphisms with the risk of osteoporosis in a Chinese population

Yakun Fan, Shiyang Zhang, Fang Liang, Yanyan Zhou

Department of Geriatrics, The First Hospital of Shijiazhuang, Shijiazhuang 050000, Hebei, China

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Abstract: Osteoporosis is a systemic metabolic and serious skeletal disease commonly observed among the elderly. Insulin-like growth factors (IGFs) are critical regulators for bone cell function. We estimated the role of IGF-I rs35767, rs2288377 and rs5742612 polymorphisms in the susceptibility to osteoporosis in a population of China, and assessed gene-environment interactions. A total of 346 patients with osteoporosis and 346 controls were enrolled. Genotyping of IGF-I rs35767, rs2288377 and rs5742612 was amplified and performed with the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The TA and AA genotypes displayed elevated risk of developing osteoporosis (TA vs TT: OR=1.54, 95% CI=1.11-2.15; AA vs TT: OR=3.65, 95% CI=2.09-6.37). Compared with TT individuals, individuals with the TA+AA genotype had a substantial increased susceptibility to osteoporosis (OR=1.80, 95% CI=1.31-2.46). In recessive model, the AA genotype of rs2288377 displayed 2.89 folds risk of osteoporosis (adjusted OR=2.89, 95% CI=1.70-4.89). A significant negative interaction was found between IGF-I rs2288377 and BMD levels for femoral neck (r=-0.14, *P*<0.001), total hip (r=-0.09, *P*<0.001) and trochanter (r=-0.13, *P*<0.001). In conclusion, we suggest that IGF-I rs2288377 polymorphism had a strong influence on osteoporosis susceptibility in this Chinese population.

Keywords: Osteoporosis, IGF-I, polymorphism, gene-environmental interaction

Introduction

Osteoporosis, a systemic metabolic and serious skeletal disease commonly observed among the elderly, is a public health problem worldwide and associated with substantial morbidity and socio-economic burden [1]. Osteoporosis can occur in both males and females at any age, but this disease is most common in older women. Osteoporosis would increase bone fragility subsequently and is susceptible to fracture, and it could influence 75 million population over the world [2]. The development of osteoporosis is correlated with various environmental and lifestyle factors, such as lack of physical activities, weight, calcium and vitamin D, and long-term consumption of alcohol drinking and coffee [3, 4]. Moreover, the role of common genetic variation in determining the range of individual susceptibility to osteoporosis within the population is increasingly recognized [5-8].

Insulin-like growth factors (IGFs) are critical regulators for bone cell function, because of the IGFs' anabolic role in the skeleton [9, 10]. The IGF system contributes to the local regulation of bone formation, and about half of the basal bone cell proliferation can be prevented through activity of IGFs intrinsically produced by the bone cells [10]. IGF-I is the target gene of estrogen, and it could influence the bone metabolism through regulation the function of estrogen [11]. Previous studies have indicated that IGF-I expression is associated with bone formation and bone loss [12, 13]. Single nucleotide polymorphisms (SNPs) can influence the gene expression and function, participating in susceptibility to diseases [14].

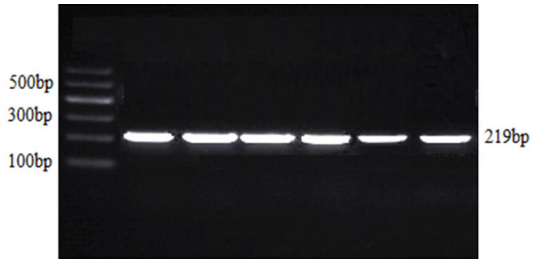

Figure 1. Electrophoresis of PCR products for IGF-1 rs2288377.

Currently, several studies have reported the correlation between IGF-I polymorphisms and susceptibility to osteoporosis, but the results remains inconsistent due to different ethnicities and gene-environmental interactions [15-19]. However, few studies reported the gene-environmental interaction between IGF-I polymorphisms and environmental factors in the development of osteoporosis. To provide a more precise evaluation of such association, we performed a 1:1 matched case-control study to estimate the role of IGF-I rs35767, rs2288377 and rs5742612 polymorphisms in the susceptibility to osteoporosis in a population of China, and assessed the gene-environment interactions.

Subjects and methods

The study protocol was approved by the Institutional Review Board of the First Hospital of Shijiazhuang, Shijiazhuang, China. All subjects involved in this study signed the informed consent and agreed to participate in this study voluntarily prior to enrollment.

Patients and controls

In this study, 346 patients with osteoporosis were enrolled, between January 2015 and June 2016, from the First Hospital of Shijiazhuang. All patients were primarily diagnosed by the criteria of the World Health Organization [20]. The diagnosis of osteoporosis was defined as individuals with a T score of bone mineral density (BMD) ≤-2.5 SD at the femoral neck without an evidence of vertebral fractures, or those with a T score of BMD≤-1.5 SD at the femoral neck with an evidence of more than two vertebral fractures. Patients with intake of drugs disturbing the balance of bone metabolism, and with a history of any digestive system diseases affecting the nutrient absorption, were excluded from this study.

Simultaneously, 346 healthy subjects, with matched age (±5 years) composition, were enrolled from normal physical examination center from the First Hospital of Shijiazhuang, and they were considered as the control group. Subjects who had a history of osteoporosis, serious endocrine diseases and digestive system diseases were excluded from the control groups. Blood samples for DNA extraction were obtained immediately after diagnosis of osteoporosis without any drugs adopt.

Determination of BMD

X-ray of the lumbar spine was used for all subjects. BMD of the lumbar spine was measured by dual-energy X-ray absorptiometry (Hologic® QDR 1000, Siemens Medical Systems, Erlangen, Germany) and determined by radiologists. The BMD was calculated by dividing bone mineral content (g) by bone area (cm^2) (g/cm^2).

Collection of demographic and clinical characteristics

The demographic and clinical variables of investigated subjects were obtained from medical records, including sex, age, body mass index (BMI), tobacco smoking and alcohol drinking habits, and BMD levels.

Genotype analyses

Genomic DNA was extracted from peripheral blood by TIANamp DNA Blood Mini Kit (QIAGEN GmbH, Germany) following with the instruction. Genotyping of IGF-I rs35767, rs2288377 and rs5742612 was amplified and performed with the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method by two operators independently and blinded. PCR-RFLP method was performed using the PCR Thermocycle Instrument (MJ Research Inc., St. Bruno, Canada). The pair of primers for IGF-I rs35767 was 5'-AGCAGCTAGATTCACAGCA-3' and 5'-TTATGTGAGCAGTAGATAAGAAGTGA-3'; for rs2288377, the primers were 5'-TCATGCTGGAACTTGACGTTG-3' and 5'-AGAACAGCAGAATGCAATCTGATTGTG-3'; for rs5742612, the primers were 5'-GCGTAGTGTAGCTATTACTGACATCGAT-3' and 5'-GTGACTGACTGTCTGTTAG-3'. Generally, DNA amplification was per-

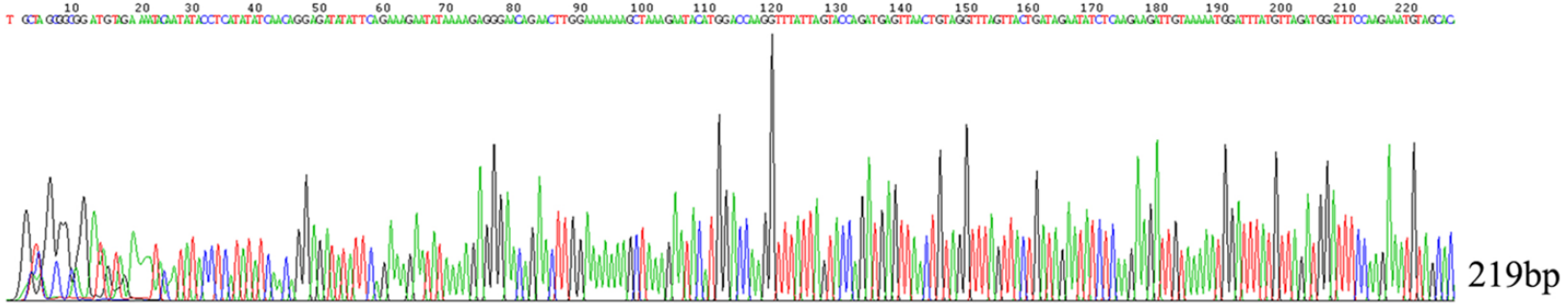

Figure 2. Sequencing of the PCR products for IGF-1 rs2288377.

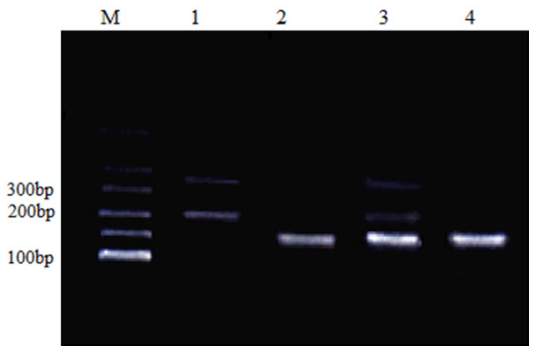

Figure 3. Electrophoregram of PCR products of digestion for IGF-1 rs2288377. M: marker (DNA ladder); lane 1 and 4: TC genotype; lane 2: TT genotype; lane 3: CC genotype.

formed in a 20-μL volume mixtures containing 10 pmol of each primer, 4.5 mmol/L $MgCl_2$, 0.25 mmol/L of each dNTP, 1 μl Taq polymerase, and 1.5 mmol/L buffer with a 94°C initial denaturation for minutes; 35 amplification cycles of 94°C for 30 seconds, 58°C for 30 seconds, and 72°C for 30 seconds; and a final 72°C extension for 7 minutes. The PCR products were analyzed in 3% agarose gel electrophoresis and observed under ethidium bromide staining (**Figures 1-4**). Approximately 10% of the samples were randomly selected for repeating for verification and validation. The repeated results were 100% concordant.

Statistical analysis

Data analysis started with descriptive statistics, including mean ± SD for continuous variables and frequency for categorical variables. Comparisons of the categorical and continuous variables between groups were analyzed by student's *t*-tests, Pearson's chi-square (χ^2) or Fisher's exact tests. Hardy-Weinberg equilibrium (HWE) of the IGF-I rs35767, rs2288377 and rs5742612 was evaluated by a goodness-of-fit chi-square test. The association of IGF-I polymorphisms with the risk of osteoporosis was evaluated using conditional logistic regression analysis, with adjustment for potential confounding factors. Three dominant, co-dominant and recessive genetic models were used for analysis. The gene-environment interaction was analyzed by Spearman correlation analysis. The statistical software of SPSS Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, USA) was applied for the analyses. An P<0.05 was used for all statistical tests.

Results

The demographic information of 346 patients with osteoporosis and 346 controls are shown in **Table 1**. Both sex and age were well-matched between patients and controls without significant differences (*P*=0.86 and 0.21, respectively). There were significant differences between patients and controls in BMI (*P*=0.01), tobacco smoking (*P*=0.03) and alcohol drinking (*P*=0.004). BMD levels in L1-L4 vertebrae, femoral neck, total hip and trochanter in patients were significantly higher than those in controls (All *P*<0.001).

The genotypes of IGF-I rs35767, rs2288377 and rs5742612 are shown in **Table 2**. The frequencies of TT, TA and AA genotypes in patients were significantly different from controls with *P*<0.001. The genotype frequencies of rs35767, rs2288377 and rs5742612 were not deviated from HWE in both patients and controls (All *P*>0.05) (Supplementary 1).

With polymorphism in co-dominant model, the TA and AA genotypes of rs2288377 displayed elevated risk of developing osteoporosis (TA vs TT: OR=1.54, 95% CI=1.11-2.15; AA vs TT: OR=3.65, 95% CI=2.09-6.37) (**Table 3**). Compared with TT individuals, individuals with the TA+AA genotype had a substantial increased susceptibility to osteoporosis (OR=1.80, 95% CI=1.31-2.46). In recessive model, the AA genotype of rs2288377 displayed 2.89 folds risk of osteoporosis (adjusted OR=2.89, 95% CI=1.70-4.89). However, we did not find significantly association between rs35767 and rs5742612 polymorphisms and osteoporosis risk in all genotype models.

We performed a gene-environment interaction analysis between IGF-I rs2288377 polymorphism and demographic and clinical characteristics in development of osteoporosis (**Tables 4** and **5**). We observed a significant negative interaction between IGF-I rs2288377 and BMD levels for femoral neck (r=-0.14, *P*<0.001), total hip (r=-0.09, *P*<0.001) and trochanter (r=-0.13, *P*<0.001).

Discussion

Single-nucleotide polymorphisms (SNPs), the most common mutations of DNA sequence variation, could affect the functional roles of

Figure 4. Sequencing for three genotypes of IGF-1 rs2288377.

Table 1. Demographic and clinical characteristics of patients with osteoporosis and controls

Variables	Patients N=346	%	Controls N=346	%	χ^2 or t values	*P* values
Sex						
Females	254	73.41	256	73.99		
Males	92	26.59	90	26.01	0.03	0.86
Age, years		68.86±9.33		69.83±9.17	0.79	0.21
BMI, kg/m^2						
<24	217	62.72	181	52.31		
≥24	129	37.28	165	47.69	7.66	0.01
Tobacco smoking habit						
No	221	63.87	248	71.68		
Yes	125	36.13	98	28.32	4.82	0.03
Alcohol drinking habit						
No	213	61.56	249	71.97		
Yes	133	38.44	97	28.03	8.44	0.004
BMD, g/cm^2						
L_1-L_4 vertebrae		0.92±0.089		0.97±0.099	7.71	<0.001
Femoral neck		0.58±0.029		0.66±0.028	37.81	<0.001
Total hip		0.60±0.036		0.65±0.039	18.55	<0.001
Trochanter		0.53±0.038		0.61±0.044	24.42	<0.001

Table 2. Genotype distributions of IGF-I genetic polymorphisms between the two investigated groups

Genotypes	Patients	%	Controls	%	χ^2 values	*P* values	*P* value for HWE	
							Patients	Controls
rs35767								
CC	154	44.51	152	43.93				
TC	163	47.11	157	45.38				
TT	29	8.38	37	10.69	1.1	0.58	0.12	0.71
rs2288377								
TT	118	34.10	164	47.40				
TA	171	49.42	160	46.24				
AA	57	16.47	22	6.36	23.38	<0.001	0.71	0.36
rs5742612								
TT	298	86.13	301	86.99				
TG	30	8.67	35	10.12				
GG	18	5.20	10	2.89	2.69	0.026	0.07	0.06

proteins in the signal transduction of visual, hormonal, and other stimulants [21]. These SNPs affect gene expression through modifying DNA and transcription factor binding. In this study, we identified and quantified the significant association between IGF-I genetic polymorphisms and osteoporosis susceptibility [22]. Our study suggested that TA and AA genotypes of IGF-I rs2288377 were significantly associated osteoporosis susceptibility in this population.

IGF-1 is an important regulator of proliferation, cell differentiation and apoptosis [23]. One experimental study has shown that IGF-I could affect the cell proliferation and differentiation of osteoprogenitor cells in normal rats, and also increase osteogenic colony number, total alkaline phosphatase (ALP) activity and total mineralization in bone marrow ostoprogenitor cells of normally loaded rats [24]. Moreover, the low expression of IGF-I in serum is reported to be associated with susceptibility to osteoporo-

Table 3. Association between IGF-I genetic polymorphisms and risk of osteoporosis by logistic regression analysis

Genotypes		Patients	%	Controls	%	Crude OR (95% CI)	*P* values	Adjusted OR (95% CI)[1]	*P* values
IGF-I									
rs35767	CC	152	47.5	156	48.75	1.0 (Ref.)	-	1.0 (Ref.)	-
Co-dominant	TC	136	42.5	131	40.94	1.03 (0.75-1.42)	0.87	1.02 (0.74-1.42)	0.89
	TT	32	10	33	10.31	0.80 (0.46-1.38)	0.42	0.71 (0.47-1.41)	0.46
Dominant	CC	152	47.5	156	48.75	1.0 (Ref.)	-	1.0 (Ref.)	-
	TC+TT	168	52.5	164	51.25	0.95 (0.70-1.28)	0.72	0.94 (0.69-1.28)	0.70
Recessive	TC+CC	288	90	287	89.69	1.0 (Ref.)	-	1.0 (Ref.)	-
	TT	32	10	33	10.31	0.78 (0.46-1.31)	0.34	0.79 (0.47-1.34)	0.38
rs2288377	TT	125	39.06	157	49.06	1.0 (Ref.)	-	1.0 (Ref.)	-
Co-dominant	TA	145	45.31	138	43.13	1.49 (1.08-2.06)	0.02	1.54 (1.11-2.15)	0.01
	AA	50	15.63	25	7.81	3.59 (2.07-6.20)	<0.001	3.65 (2.09-6.37)	<0.001
Dominant	TT	125	39.06	157	49.06	1.0 (Ref.)	-	1.0 (Ref.)	-
	TA+AA	195	60.94	163	50.94	1.75 (1.28-2.37)	<0.001	1.80 (1.31-2.46)	<0.001
Recessive	TA+TT	270	84.37	295	92.19	1.0 (Ref.)	-	1.0 (Ref.)	-
	AA	50	15.63	25	7.81	2.90 (1.73-4.86)	<0.001	2.89 (1.70-4.89)	<0.001
rs5742612	TT	264	82.5	275	85.94	1.0 (Ref.)	-	1.0 (Ref.)	-
Co-dominant	TG	33	10.31	29	9.06	0.87 (0.51-1.46)	0.59	0.89 (0.53-1.52)	0.67
	GG	23	7.19	16	5.00	1.81 (0.81-4.05)	0.15	1.91 (0.84-4.35)	0.12
Dominant	TT	264	82.5	275	85.94	1.0 (Ref.)	-	1.0 (Ref.)	-
	TG+GG	56	17.5	45	14.06	1.05 (0.68-1.64)	0.82	1.08 (1.31-2.46)	0.72
Recessive	TC+TT	297	92.81	304	95.00	1.0 (Ref.)	-	1.0 (Ref.)	-
	GG	23	7.19	16	5.00	1.79 (0.81-3.98)	0.15	1.87 (0.83-4.25)	0.13

[1]Adjusted for BMI, tobacco smoking and alcohol drinking.

Table 4. Interaction between the rs2288377 and smoking, drinking and BMI in the risk of osteoporosis

Variables	rs2288377	
	Correlation coefficient	*P* values
BMI	-0.006	0.87
Tobacco smoking	-0.032	0.40
Alcohol drinking	0.045	0.24

Table 5. Interaction between the rs2288377 and BMD levels in the risk of osteoporosis

Variables	rs2288377	
	r	*P* values
BMD for L_1-L_4 vertebrae	-0.04	0.30
BMD for femoral neck	-0.14	<0.001
BMD for total hip	-0.09	<0.001
BMD for trochanter	-0.13	<0.001

sis, and is also correlated with lower bone mineral density [25-28].

A major interest in human genetics is to distinguish genetic mutations that are functionally from those that contribute to diseases. Identification of gene polymorphisms that influence the functions and expression of proteins and relate to disease is an critical task. Currently, amino acid substitutions are responsible for about 50% of the known gene lesions responsible for genetically determined diseases. SNPs that change the amino acids might play an important role in affect the susceptibility to diseases [29]. Polymorphisms in IGF-I could directly influence the expression of IGF-I, and many epidemiologic studies have reported the IGF-1 promoter polymorphisms could influence risk of many diseases through alteration of gene expression [22, 30, 31].

For the correlation between IGF-I polymorphisms and susceptibility to osteoporosis, several previous studies have reported contradictory results [16, 19, 32-35]. Three studies have shown that IGF-I rs35767 polymorphism significantly influences the bone mineral density and risk of osteoporosis among females [16, 19, 34]. Kim et al. reported that IGF-I 194-base pair allele significantly affect the bone mineral density among Korean females [32]. However,

Jiang et al. performed a large sample size study in a Chinese population, but they did not find an association between IGF-I gene and BMD variation among premenopausal in a Chinese population [33]. In this study, we only observed a correlation between IGF-I rs2288377 polymorphism and risk of osteoporosis, and a significant interaction between IGF-I rs2288377 and BMD levels in the Chinese population. Therefore, results concerning the association of IGF-I rs2288377 polymorphism with the risk of osteoporosis are not consistent, principally owing to the differences in environmental factors, ethnicity and genetic background.

Nevertheless, some limitations of this study should be mentioned. First, only 346 patients were enrolled. The relatively small sample size might lead to a lower statistical power in this study. Second, rs35767, rs2288377 and rs5742612 was not the only polymorphisms in IGF-1, and the comprehensive analysis among SNPs needs to be carried out in future studies to investigate their potential interactions.

In conclusion, we suggest that IGF-I rs2288377 polymorphism had a strong influence on osteoporosis susceptibility, and a negative interaction between IGF-I rs2288377 and BMD levels for femoral neck, total hip and trochanter in this Chinese population. Further multi-center and well designed studies among different ethnic groups are warranted to confirm our findings.

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Disclosure of conflict of interest

None.

Address correspondence to: Can Zhang, Department of Geriatrics, The First Hospital of Shijiazhuang, No. 36 Fanxi Road, Chang'an District, Shijiazhuang 050000, Hebei, China. E-mail: canzhangc@126.com

References

[1] Rachner TD, Khosla S and Hofbauer LC. Osteoporosis: now and the future. Lancet 2011; 377: 1276-1287.

[2] Hadji P, Klein S, Gothe H, Haussler B, Kless T, Schmidt T, Steinle T, Verheyen F and Linder R. The epidemiology of osteoporosis--Bone Evaluation Study (BEST): an analysis of routine health insurance data. Dtsch Arztebl Int 2013; 110: 52-57.

[3] Wu J, Shang DP, Yang S, Fu DP, Ling HY, Hou SS and Lu JM. Association between the vitamin D receptor gene polymorphism and osteoporosis. Biomed Rep 2016; 5: 233-236.

[4] Cappola AR and Shoback DM. Osteoporosis therapy in postmenopausal women with high risk of fracture. JAMA 2016; 316: 715-716.

[5] Yu M, Chen GQ and Yu F. Lack of association between vitamin D receptor polymorphisms ApaI (rs7975232) and BsmI (rs1544410) and osteoporosis among the Han Chinese population: a meta-analysis. Kaohsiung J Med Sci 2016; 32: 599-606.

[6] Wu J, Shang DP, Yang S, Fu DP, Ling HY, Hou SS and Lu JM. Association between the vitamin D receptor gene polymorphism and osteoporosis. Biomed Rep 2016; 5: 233-236.

[7] Guo L, Tang K, Quan Z, Zhao Z and Jiang D. Association between seven common OPG genetic polymorphisms and osteoporosis risk: a meta-analysis. DNA Cell Biol 2014; 33: 29-39.

[8] Wegner M, Mostowska A, Araszkiewicz A, Choudhury M, Piorunska-Stolzmann M, Zozulinska-Ziolkiewicz D, Wierusz-Wysocka B and Jagodzinski PP. Association investigation of BACH2 rs3757247 and SOD2 rs4880 polymorphisms with the type 1 diabetes and diabetes long-term complications risk in the Polish population. Biomed Rep 2015; 3: 327-332.

[9] McCarthy TL, Centrella M and Canalis E. Insulin-like growth factor (IGF) and bone. Connect Tissue Res 1989; 20: 277-282.

[10] Mohan S. Insulin-like growth factor binding proteins in bone cell regulation. Growth Regul 1993; 3: 67-70.

[11] Kassem M, Okazaki R, Harris SA, Spelsberg TC, Conover CA and Riggs BL. Estrogen effects on insulin-like growth factor gene expression in a human osteoblastic cell line with high levels of estrogen receptor. Calcif Tissue Int 1998; 62: 60-66.

[12] Simental-Mendia M, Lara-Arias J, Alvarez-Lozano E, Said-Fernandez S, Soto-Dominguez A, Padilla-Rivas GR and Martinez-Rodriguez HG. Cotransfected human chondrocytes: over-expression of IGF-I and SOX9 enhances the synthesis of cartilage matrix components collagen-II and glycosaminoglycans. Braz J Med Biol Res 2015; 48: 1063-1070.

[13] Livingstone C and Borai A. Insulin-like growth factor-II: its role in metabolic and endocrine disease. Clin Endocrinol (Oxf) 2014; 80: 773-781.

[14] Gaffney DJ. Global properties and functional complexity of human gene regulatory variation. PLoS Genet 2013; 9: e1003501.

[15] Wei YK, Ma HL, Guo YZ, Yang BH and Pang WX. Association of the IGF-1 rs35767 and rs972936 polymorphisms with the risk of osteoporosis in a Chinese postmenopausal fe-

male population. Genet Mol Res 2015; 14: 14325-14330.
[16] Zhang W, Zhang LC, Chen H, Tang PF and Zhang LH. Association between polymorphisms in insulin-like growth factor-1 and risk of osteoporosis. Genet Mol Res 2015; 14: 7655-7660.
[17] Li N, Zhang C, Chen Z, Bai L, Nie M, Zhou B and Xu H. Interleukin 17A and interleukin 17F polymorphisms are associated with oral squamous cell carcinoma susceptibility in a Chinese population. J Oral Maxillofac Surg 2015; 73: 267-273.
[18] Li F, Xing WH, Yang XJ, Jiang HY and Xia H. Influence of polymorphisms in insulin-like growth factor-1 on the risk of osteoporosis in a Chinese postmenopausal female population. Int J Clin Exp Pathol 2015; 8: 5727-5732.
[19] Yun-Kai L, Hui W, Xin-Wei Z, Liang G and Jin-Liang Z. The polymorphism of Insulin-like growth factor-I (IGF-I) is related to osteoporosis and bone mineral density in postmenopausal population. Pak J Med Sci 2014; 30: 131-135.
[20] Aronow WS. Osteoporosis, osteopenia, and atherosclerotic vascular disease. Arch Med Sci 2011; 7: 21-26.
[21] Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lubahn DB and Korach KS. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994; 331: 1056-1061.
[22] Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, Chatterjee VK and O'Rahilly S. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 1999; 402: 880-883.
[23] Costa-Silva DR, Barros-Oliveira MD, Borges RS, Tavares CB, Borges US, Alves-Ribeiro FA, Silva VC and Silva BB. Insulin-like growth factor 1 gene polymorphism and breast cancer risk. An Acad Bras Cienc 2016; 88: 2349-2356.
[24] Sakata T, Halloran BP, Elalieh HZ, Munson SJ, Rudner L, Venton L, Ginzinger D, Rosen CJ and Bikle DD. Skeletal unloading induces resistance to insulin-like growth factor I on bone formation. Bone 2003; 32: 669-680.
[25] Mezquita-Raya P, Muñoz-Torres M, Alonso G, de Luna JD, Quesada JM, Dorado G, Luque-Recio F, Ruiz-Requena ME, Lopez-Rodriguez F and Escobar-Jiménez F. Susceptibility for postmenopausal osteoporosis: interaction between genetic, hormonal and lifestyle factors. Calcif Tissue Int 2004; 75: 373-379.
[26] Mochizuki S, Yoshida S, Yamanaka Y, Matsuo H and Maruo T. Effects of estriol on proliferative activity and expression of insulin-like growth factor-I (IGF-I) and IGF-I receptor mRNA in cultured human osteoblast-like osteosarcoma cells. Gynecol Endocrinol 2005; 20: 6-12.
[27] Nakayama Y, Nakajima Y, Kato N, Takai H, Kim DS, Arai M, Mezawa M, Araki S, Sodek J and Ogata Y. Insulin-like growth factor-I increases bone sialoprotein (BSP) expression through fibroblast growth factor-2 response element and homeodomain protein-binding site in the proximal promoter of the BSP gene. J Cell Physiol 2006; 208: 326-335.
[28] McCarthy TL, Yun Z, Madri JA and Centrella M. Stratified control of IGF-I expression by hypoxia and stress hormones in osteoblasts. Gene 2014; 539: 141-151.
[29] Masoodi TA, Alsaif MA, Al Shammari SA and Alhamdan AA. Evaluation and identification of damaged single nucleotide polymorphisms in COL1A1 gene involved in osteoporosis. Arch Med Sci 2013; 9: 899-905.
[30] de Groot S, Charehbili A, van Laarhoven HW, Mooyaart AL, Dekker-Ensink NG, van de Ven S, Janssen LG, Swen JJ, Smit VT, Heijns JB, Kessels LW, van der Straaten T, Bohringer S, Gelderblom H, van der Hoeven JJ, Guchelaar HJ, Pijl H and Kroep JR. Insulin-like growth factor 1 receptor expression and IGF1R 3129G > T polymorphism are associated with response to neoadjuvant chemotherapy in breast cancer patients: results from the NEOZOTAC trial (BOOG 2010-01). Breast Cancer Res 2016; 18: 3.
[31] Bhattacharya TK, Chatterjee RN, Dushyanth K, Paswan C, Shukla R and Shanmugam M. Polymorphism and expression of insulin-like growth factor 1 (IGF1) gene and its association with growth traits in chicken. Br Poult Sci 2015; 56: 398-407.
[32] Kim JG, Roh KR and Lee JY. The relationship among serum insulin-like growth factor-I, insulin-like growth factor-I gene polymorphism, and bone mineral density in postmenopausal women in Korea. Am J Obstet Gynecol 2002; 186: 345-350.
[33] Jiang DK, Li MX, Jiang C, Yang N, Zhu J, Wu Y, Qin YJ, Zhou Q and Deng HW. No major effect of the insulin-like growth factor I gene on bone mineral density in premenopausal Chinese women. Bone 2005; 36: 694-699.
[34] Li SM, Guo H, Yang HJ, Lv MQ and Zhou DX. HLA-A gene polymorphisms contribute to osteoporosis susceptibility in postmenopausal Han Chinese women. Genet Mol Res 2015; 14: 10322-10330.
[35] Niu T and Rosen CJ. The insulin-like growth factor-I gene and osteoporosis: a critical appraisal. Gene 2005; 361: 38-56.