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Association of Adrenergic Receptor α2A (α2A-AR) Gene rs1800544 Polymorphism with Bone Mineral Density and Bone Turnover Markers in an Elderly Chinese Population

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Qi-Fei Wang
BC 2 Zhe Sun
BF 1 Fan-Rong Zheng
AEG 1 Guang-Wu Zhang
AF 1 Zheng Liu

1 Department of Orthopedics, Peking University Shougang Hospital, Beijing, P.R. China
2 Department of Orthopedics, Zibo Central Hospital, Zibo, Shandong, P.R. China

Corresponding Author: Zheng Liu, e-mail: 953997296@qq.com
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Background: Adrenergic receptor α2A (α2A-AR) is up-regulated in osteoporotic bone osteoblasts. Previous research demonstrated an association between polymorphism of α2A-AR gene and bone mineral density (BMD) as well as bone turnover markers (BTMs) in the Slovenian population. The present study aimed to investigate the association of rs1800544 polymorphism of α2A-AR gene with BMD and BTMs in the Chinese elderly population with osteoporosis (OP) or with osteoporotic fractures.

Material/Methods: A total of 346 unrelated elderly individuals were recruited in the study. Rs1800544 polymorphism was determined by Snapshot technology. BTMs were determined by electrochemiluminescence. BMDs at lumbar spine (LS) and proximal femur were measured with dual-energy X-ray absorptiometry (DEXA). Hardy-Weinberg equilibrium and distribution of genotype frequencies were verified using the chi-squared test. Analysis of co-variance (ANCOVA) adjusted for confounding factors was performed to explore the relationship of rs1800544 polymorphism with BMD and BTMs in all participants and in subgroups.

Results: The genotype distributions in all subjects and in subgroups conformed to Hardy-Weinberg equilibrium (P>0.1). Distribution of genotype frequencies of subgroups showed no significant differences (P>0.05). Patients with GG genotype in the fracture group had significantly higher serum BTMs level compared with those carrying other genotypes (P<0.05). No significant association between rs1800544 and BTMs was detected in the elderly population with OP. Comparison of BMD at each site in all participants did not show any significant difference in subgroups with CC, CG, and GG genotypes (P>0.05).

Conclusions: Rs1800544 polymorphism is associated with BTMs level in Chinese elderly individuals with osteoporotic fractures, indicating the involvement of genetic variation of α2A-AR gene in bone metabolism.

MeSH Keywords: Biological Markers • Bone Density • Osteoporotic Fractures • Polymorphism, Single Nucleotide

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Background

OP is a systemic skeletal disorder characterized by reduced bone mass, disturbed microarchitecture of bone tissue, increased bone fragility, and susceptibility to fractures [1,2]. The condition is highly prevalent in postmenopausal women and the elderly population. The morbidity burden attributable to OP is liable to increase with population aging. The absolute number of patients affected by OP in China is projected to increase to 210 million by 2050. Osteoporotic fractures in elderly people are associated with a poor prognosis [3–5]. For instance, mortality rates in aged patients who sustain hip fractures may reach as high as 20% at 1 year. Hence, OP constitutes a major public health problem [1,6]. The etiology of OP is multifactorial; environmental, life-style, and genetic factors have been shown to play a key role in its pathogenesis [7–10]. Genetic factors are believed to account for 60–80% of individual variance in BMD [11], which is a known predictor of the risk of osteoporotic fractures [1, 12]. Estrogen receptor (ER) gene [13,14], vitamin D receptor (VDR) gene [15,16], genes of the RANKL-RANK-OPG system [17], and genes that regulate the synthesis of transforming growth factor-β1 (TGF-β1) [18,19] have been reported as potential determinants of bone mass at the population level.

α2A-AR is up-regulated in osteoblasts and plays a key role in the development of OP. An animal study demonstrated that female mice with the double adrenoreceptor removed presented an increased bone density phenotype. A common polymorphism rs1800544 located in α2A-AR gene showed an association with diverse phenotypes, including tobacco smoking [20], adolescent personality [21], and olanzapine treatment [22]. In addition, the association of α2A-AR gene polymorphism with BMD as well as BTMs has been reported in the Slovenian population [23]. Mlakar et al. [23] revealed that carriers of GC genotype of rs1800544 had a slightly higher BMD at LS as compared to that in carriers of GG genotype in a cohort of 429 postmenopausal women. In addition, elderly men carrying GC genotype had significantly higher serum C-terminal crosslinking telopeptides of type I collagen than those with CC genotype. Although the study SNPs were proven to be involved in regulating bone metabolism, the conclusion may not apply to other ethnicities and populations due to genetic variations and diverse environmental factors.

In the present study, we aimed to investigate genotype distributions of rs1800544 in fracture and osteoporotic groups and to explore the correlation of rs1800544 polymorphism in the α2A-AR gene with BTMs and BMD in a cohort of elderly people with osteoporotic fractures or with OP in China. The findings would increase understanding of the influence of the α2A-AR gene on bone metabolism.

Material and Methods

Participants

This prospective study enrolled a total of 346 unrelated participants, including 183 patients with osteoporotic fractures and 163 patients with OP attending the Orthopedics Department, the Gerontology Department, and the Endocrine Department of Beijing University Shougang Hospital from December 2015 to May 2017. All participants were consecutive patients recruited at the hospital. Participants with osteoporotic fractures were considered the fracture group, which consisted of 126 females and 57 males (mean age 76.7±7.3 years). Subjects with OP were regarded as the osteoporotic group, which comprised 104 females and 59 males (mean age 72.3±7.4 years). The osteoporotic group was the control group and the 2 groups were matched by age, sex, and body mass index (BMI). Participants with T-score at any site ≤–2.5 were considered osteoporotic based on the World Health Organization (WHO) criteria. All osteoporotic fractures occurred under low trauma in the last week before enrollment. All subjects underwent clinical examinations and routine biochemical tests to exclude patients who had systemic or metabolic bone diseases, such as cardiovascular, hepatic, or renal disorders and secondary OP, instead of primary OP. None of the patients had previously taken any drug known to interfere with bone metabolism in the last 2 years (6 female participants in the fracture group had been treated with estradiol valerate tablets (1–2 mg/d) or raloxifene hydrochloride tablets (60 mg/d) for 2–3years when they were diagnosed as having postmenopausal osteoporosis (PMOP) 5 years before their enrollments. They had stopped treatment for more than 2 years. None of the subjects in the osteoporotic group had been treated with any drug affecting bone turnover, and all of them were first diagnosed as having osteoporosis. The research design conformed to the principles of the Declaration of Helsinki. The study was approved by the Institutional Ethics Committee. Participation in the study was purely voluntary and written informed consent was obtained from all subjects prior to their enrollment.

BTMs measurement

Blood samples of all subjects were collected from cubital veins in the morning. Procollagen type I carboxy terminal peptide beta special sequence (β-CTX) and procollagen I N-terminal propeptide (PINP) were measured with electrochemiluminescence assay using kits from Roche Laboratory (Mannheim, Germany) according to the manufacturer's instructions.

Bone mineral density measurement

BMD at the femoral neck (FN), femoral trochanter (FT), Ward's triangle (WT), total hip (TH), and LS at the L2, L3, L4, and L2–L4

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Table 1. Characteristics of participants disaggregated by study group.

Variables	Fractures group mean ±SD	Osteoporotic group mean ±SD	P
Age (years)	76.7±7.3	72.3±7.4	0.237
Female/male	126/57	104/59	0.321
BMI (kg/m^2)	20.467±2.821	22.633±2.462	0.352
β-CTX (ng/mL)	0.471±0.361	0.454±0.250	0.952
PINP (ng/ml)	54.312±34.92	48.856±29.300	0.221
BMD L2 (g/cm^2)	0.703±0.162	0.724±0.345	<0.001
BMD L3 (g/cm^2)	0.715±0.159	0.733±0.298	0.243
BMD L4 (g/cm^2)	0.697±0.190	0.721±0.283	0.002
BMD L2–L4 (g/cm^2)	0.712±0.174	0.726±0.249	<0.001
BMD FN (g/cm^2)	0.612±0.133	0.652±0.195	0.235
BMD WT (g/cm^2)	0.422±0.238	0.481±0.213	0.334
BMD FT (g/cm^2)	0.537±0.129	0.568±0.216	<0.001
BMD TH (g/cm^2)	0.727±0.203	0.761±0.243	0.241

BMI – body mass index; β-CTX – procollagen type I carboxy terminal peptide beta special sequence; PINP – procollagen I N-terminal propeptide; BMD – bone mineral density; L2 – L2 vertebra; L3 – L3 vertebra; L4 – L4 vertebra; L2–L4 – L2–L4 vertebra; FN – femoral neck; WT – Ward's triangle; FT – femoral trochanter; TH – total hip. All P values excluding age female and BMI were adjusted for age and BMI by ANCOVA.

levels were measured in all participants by DEXA (QDR-4500; HOLOGIC, Inc., Bedford, MA, USA). Additionally, body height and weight were measured to calculate BMI (kg/m^2). The instrument was calibrated daily in accordance with the manufacturer's instructions. BMD values were expressed as grams per cm^2. The criterion used for diagnosis of OP was T-score at the FN or LS ≤–2.5.

Genotyping

In the morning, 2 ml of fasting venous blood was collected in EDTA-containing tubes, and genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany). DNA was stored at –80°C until genotyped. Polymorphism of rs1800544 was determined by Snapshot technology. The primers of rs1800544, including upstream primer: 5'-TCTGTTCACAAAACATGGAATTAG-3' and downstream primer: 5'-AAGAGACTGATGACACCGTGACAG-3', were synthesized by Shanghai Biological Engineering Technology Co., Ltd. Genotyping was completed by Beijing Microread Gene Technology Co., Ltd. The sensitivity and specificity of the Snapshot method, which was the best genotyping method except for the criterion standard, direct sequencing, were 99.8% and 99.9%, respectively.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (S.D.) and categorical variables are expressed as frequencies and percentages. Deviation from Hardy-Weinberg equilibrium for 2A-AR gene was estimated by chi-squared test. Value of P>0.05 indicated HWEA. The Kolmogorov-Smirnov and Levene tests were performed to examine normal distribution and homogeneity of variance, respectively. Categorical variables between groups were tested by χ^2 testing. Between-group differences with respect to normally distributed continuous variables were assessed with analysis of co-variance (ANCOVA) adjusted for confounding factors. Those with respect to non-normally distributed variables were assessed with non-parametric Kruskal Wallis test. P<0.05 was considered as statistically significant. During the period of study design, according to related literatures published and by the special software PASS 14, we found that with a sample size of 97 osteoporotic fractures and 97osteoporosis cases, the study would have more than 80% power to detect a significant difference between BTMs levels and BMD values. After data analysis and based on α, number, and mean of each group, standard deviation of subjects, number of covariate and R^2, we had 81.2% statistical power to conclude the statistically significant result by PASS 14.

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Table 2. Distributions of allele and genotype frequencies in the study population.

Group	Allele		Genotype			P-HWE
	C	G	CC	CG	GG	
Fracture group	137 (37.4%)	229 (62.6%)	30 (16.4%)	77 (42.1%)	76 (41.5%)	0.169
Control group	120 (36.8%)	206 (63.2%)	20 (12.3%)	80 (49.1%)	63 (38.6%)	0.482
Total	257 (37.1%)	435 (62.9%)	50 (14.5%)	157 (45.4%)	139 (40.1%)	0.600

Table 3. Association of rs1800544 genotype with BTMs and BMD in the study population.

Variables	CC	GC	GG	P
β-CTX (ng/mL)	0.464±0.282	0.464±0.335	0.465±0.296	0.908
PINP (ng/ml)	48.157±23.547	51.836±36.635	53.035±29.713	0.353
BMD L2 (g/cm^2)	0.726±0.254	0.718±0.226	0.696±0.249	0.748
BMD L3 (g/cm^2)	0.747±0.261	0.726±0.256	0.714±0.228	0.483
BMD L4 (g/cm^2)	0.727±0.261	0.719±0.310	0.704±0.300	0.837
BMD L2–L4 (g/cm^2)	0.731±0.254	0.721±0.278	0.709±0.261	0.687
BMD FN (g/cm^2)	0.644±0.115	0.630±0.172	0.635±0.192	0.774
BMD WT (g/cm^2)	0.411±0.162	0.455±0.167	0.475±0.364	0.438
BMD FT (g/cm^2)	0.541±0.099	0.551±0.151	0.552±0.162	0.462
BMD TH (g/cm^2)	0.694±0.167	0.725±0.149	0.778±0.274	0.673

BTMs – bone turnover markers. All P values were adjusted for age and BMI by ANCOVA.

Results

Basic characteristics of participants

Patient characteristics are summarized in Table 1. We analyzed as separate groups the BMD and BTMs of women *vs.* men. They had similar BTMs levels and BMD values (P>0.05). Hence, they were analyzed as a single group. Statistically significant between-group differences were observed with respect to BMD at L2, L4, L2–L4, and FT (P<0.05 for all adjusted for age and BMI by ANCOVA). Patients with osteoporotic fractures were found to have higher average serum PINP and β-CTX levels than those with OP; however, the differences were not statistically significant.

The distributions of allele and genotype frequencies

The distributions of allele and genotype frequencies in fracture and control groups are described in Table 2. The genotype distribution in the overall study population, and that in fracture and control groups conformed to Hardy-Weinberg equilibrium (P-values: 0.600, 0.169 and 0.482, respectively). On genotyping for rs1800544 polymorphism, the frequency of G allele accounted for 0.628 in our cohort of elderly individuals. Furthermore, GC heterozygous individuals were more common (45.4%) than those homozygous for GG (40.1%) and CC (14.5%). The rs1800544 genotype frequencies detected in the fracture group were 16.4% CC, 42.1% GC, and 41.5% GG, respectively. Which were similar to that in the osteoporotic group with 12.3% CC, 49.1% GC, and 38.6% GG. However, no statistically significant difference was observed in the distributions of allele and genotype frequencies between the elderly people with osteoporotic fractures and those with OP.

Association of rs1800544 with BTMs and BMD in the study population

Elderly with GG genotype had higher BTMs levels than those with GC and CC genotypes. BMD at LS in subjects with CC genotype were higher than that in subjects with other genotypes. However, the differences were not statistically significant (adjusted for age and BMI). No association of rs1800544 genotype with BTMs or BMD at any of the study locations was observed in all participants (P>0.05 by adjusting for age and BMI by ANCOVA) (Table 3).

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Table 4. Association of rs1800544 genotype with BTMs and BMD in fracture group.

Variables	CC	GC	GG	P
β-CTX (ng/mL)	0.475±0.334	0.474±0.393	0.479±0.343	0.656
PINP (ng/ml)	51.747±16.241	53.574±41.619	58.418±32.713	0.013*
BMD L2 (g/cm²)	0.719±0.137	0.714±0.188	0.684±0.154	0.960
BMD L3 (g/cm²)	0.740±0.134	0.721±0.164	0.705±0.174	0.901
BMD L4 (g/cm²)	0.713±0.120	0.712±0.257	0.685±0.155	0.861
BMD L2–L4 (g/cm²)	0.720±0.124	0.717±0.168	0.693±0.155	0.971
BMD FN (g/cm²)	0.614±0.102	0.600±0.143	0.605±0.132	0.970
BMD WT (g/cm²)	0.371±0.140	0.415±0.149	0.445±0.333	0.794
BMD FT (g/cm²)	0.515±0.084	0.539±0.130	0.526±0.132	0.903
BMD TH (g/cm²)	0.674±0.145	0.707±0.137	0.746±0.260	0.691

All P value were adjusted for age and BMI by ANCOVA. * GG *vs.* CC P<0.001; GG *vs.* GC P=0.008; GC *vs.* CC P=0.236 by post hoc Bonferroni test.

Table 5. Association of rs1800544 genotype with BTMs and BMD in osteoporotic group.

Variables	CC	GC	GG	P
β-CTX (ng/mL)	0.447±0.176	0.455±0.277	0.452±0.233	0.881
PINP (ng/ml)	46.694±33.971	50.295±31.902	46.686±24.655	0.842
BMD L2 (g/cm²)	0.738±0.227	0.725±0.342	0.709±0.331	0.448
BMD L3 (g/cm²)	0.751±0.211	0.736±0.287	0.723±0.265	0.565
BMD L4 (g/cm²)	0.729±0.143	0.722±0.398	0.719±0.386	0.785
BMD L2–L4 (g/cm²)	0.739±0.174	0.728±0.269	0.718±0.324	0.601
BMD FN (g/cm²)	0.667±0.135	0.653±0.189	0.649±0.219	0.773
BMD WT (g/cm²)	0.435±0.178	0.474±0.167	0.495±0.274	0.601
BMD FT (g/cm²)	0.563±0.116	0.579±0.177	0.552±0.198	0.678
BMD TH (g/cm²)	0.712±0.218	0.755±0.199	0.783±0.297	0.536

All P value were adjusted for age and BMI by ANCOVA.

Association of rs1800544 genotype with BTMs and BMD in the 2 groups

The relationship between polymorphism of rs180054 in α2A-AR gene and BTMs and BMD among the elderly with osteoporotic fractures is summarized in Table 4. Patients with GG genotype in the fracture group had significantly higher serum PINP levels as compared to that in patients with other genotypes (P=0.013 adjusted for age and BMI by ANCOVA). In addition, carriers with CC genotype had higher BMD at LS and carriers with GG genotype had higher BMD at WT and TH. However, the differences were not statistically significant (P>0.05 adjusted for age and BMI by ANCOVA). The association between rs1800544 and BTMs and BMD in the osteoporotic group is shown in Table 5. Comparison of BMD values at proximal femur and BTMs did not show any significant difference between osteoporotic patients with CC, GC, and GG genotypes.

In summary, rs1800544 polymorphism was associated with serum PINP level in the osteoporotic fracture group and was not related to BTMs levels or BMD values in the osteoporotic group.

Discussion

OP is a polygenetic disorder [24,25]. Numerous genes, including low-density lipoprotein receptor-related protein 5 (LRP5), IGF-I, and VDR genes, have been shown to be involved in the

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regulation of bone metabolism [26–29]. A previous study demonstrated the involvement of α2A-AR gene in the neuro-endocrinal signaling pathways involved in bone metabolism [23]. Rs1800544 polymorphism of the α2A-AR gene was proven to be associated with BMD-LS in postmenopausal women and with mean serum CTX levels in the elderly. In the present study, we explored the association of rs1800544 polymorphism of the α2A-AR gene with BTMs and BMD in a cohort of elderly people, including 121 patients with osteoporotic fractures and 114 osteoporotic subjects in China.

Statistically significant differences in BMD at L2, L4, L2–L4, and FT were observed between the fracture and osteoporotic groups (P<0.05 adjusted for age and BMI by ANCOVA). This was consistent with the reported association between lower BMD and risk of osteoporotic fractures [30,31]. Patients with osteoporotic fractures were found to have higher average serum levels of PINP and β-CTX level as compared to that in patients with OP. The results were supported by published literature which suggested that subjects with fractures had higher bone turnover rate [32–34]. However, the difference described in the present study was not statistically significant.

The rs1800544 genotype frequencies observed in the study population were 14.5% CC homozygotes, 45.4% GC heterozygotes, and 40.1% GG homozygotes, with 37.1% and 62.9% C and G allele frequencies, respectively. The C and G allele frequency of rs1800544 described in HapMap are 45.7% and 54.3%. No significant difference in allele and genotype frequencies was found between our study and HapMap (P-allele=0.196, P-genotype=0.800). However, genotype frequencies differed from those reported in the Slovenian population [23]. The distribution of rs1800544 genotype of 661 subjects, including premenopausal women, postmenopausal women, elderly men, and OP patients, evaluated by Mlakar et al. were as follows: CC413 (62.5%), GC 216 (32.7%), and GG 32 (4.8%), respectively. In addition, the allele frequencies of the rs1800544 in the overall study population were different from those reported earlier (72.8% C and 21.2% G). Gene mutation, population migration, natural selection, and variations in ethnicity and geographical regions may explain the marked differences in distributions of genotype and allele frequencies observed in the present study and in previous reports.

To the best of our knowledge, this is the first study to comprehensively investigate the relationship of rs1800544 polymorphism of α2A-AR gene with BTMs and BMD in a cohort of elderly subjects with OP and patients with osteoporotic fractures. Elderly subjects carrying GG genotype had higher BTMs levels than those in subjects with GC and CC genotypes. In addition, BMD at LS in subjects with CC genotype was higher than that in subjects with other genotypes.

In this study, we also compared the association of rs1800544 polymorphism with BTMs and BMD of patients in the fracture group and osteoporotic group. Interestingly, patients with GG genotype in the fracture group had significantly higher serum BTMs level compared with those carrying other genotypes (P<0.05). In addition, carriers with CC genotype had higher BMD at LS and carriers with GG genotype had higher BMD at WT and TH. However, the between-group difference was not statistically significant (P>0.05). BTMs do not necessarily demonstrate a significant change, in that the marker moieties may be modulated by different metabolic pathways (e.g., renal or hepatic), have different range of diurnal variation, and disparate coefficients of variation for their assay [35,36]. Comparison of BMD values at proximal femur and BTMs did not show any significant difference between osteoporotic patients with CC, GC, and GG genotypes. Conclusively, rs1800544 in α2A-AR gene was related with serum PINP concentration in fracture group and not associated to BTMs levels or BMD values in the osteoporotic group. Hence, we may conclude that rs1800544 SNP has a significant role in the regulation of bone metabolism in Chinese elderly people with osteoporotic fractures.

Our findings were inconsistent with a previous study[23]. Mlakar et al. determined that the α2A-AR gene played a crucial role in the neuro-endocrine regulation of bone remodeling. They reported higher BMD values at LS in postmenopausal female carriers with rs1800544 polymorphism of the GC genotype as compared to those carrying GG genotype (P=0.027). In addition, average serum CTX level was higher in the elderly with GC genotype as compared to that in the CC genotype (P=0.012). However, mean serum CTX level in the elderly with GC genotype was slightly lower compared to AA and GG genotypes in the fractures group. Genetic variation largely accounts for the discrepancy between the present and the previous study. In addition, dietary calcium and vitamin D intake, lifestyles, physical activities, and exposure to sunshine are responsible for the remarked difference observed in our study and the previous data. Due to limited published literature on the association between the α2A-AR gene and bone mass, more comparisons could not be performed.

There were several limitations in our study. Firstly, the sample size in the study was modest, which limits the statistical power to detect subtle effects [24]. Secondly, we did not include data on dietary calcium and vitamin D intake and life-style-related variables e.g., (alcohol intake, smoking, and physical activity levels) in the analysis. Another limitation is that elderly people without OP were not enrolled in the present study because there were too few participants with normal bone mass or osteopenia, especially aged individuals above age 75 years to match with the fracture or osteoporotic group by age and BMI. However, the study population was ethnically homogenous and subjects shared similar environment and lifestyles.

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Conclusions

In conclusion, a statistically significant association of rs1800544 polymorphism of the α2A-AR gene with BTMs but not BMD was observed in a cohort of elderly subjects with osteoporotic fractures, but no significant association between rs1800544 and BTMs and BMD values was detected in the elderly population with OP. Furthermore, our results suggest that the distribution of the rs1800544 genotype may show marked variability between different ethnic groups and subjects from different geographical regions. However, further functional studies are required to investigate the effect of rs1800544 polymorphism of the α2A-AR gene in the regulation of bone mass. In addition, the association between gene polymorphism and clinical efficacy of anti-osteoporosis drugs requires further study.

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Conflict of interest

None.

References:

1. Styrkarsdottir U, Thorleifsson G, Gudjonsson SA et al: Sequence variants in the PTCH1 gene associate with spine bone mineral density and osteoporotic fractures. Nat Commun, 2016; 7: 10129
2. Zha X, Hu Y, Pang X et al: The association between sex hormone-binding globulin gene polymorphism with bone mineral density. Steroids, 2016; 106: 9–18
3. Li G, Papaioannou A, Thabane L et al: Frailty change and major osteoporotic fracture in the elderly: Data from the global longitudinal study of osteoporosis in women 3-year hamilton cohort. J Bone Miner Res, 2016; 31: 718–24
4. Bliuc D, Nguyen ND, Nguyen TV et al: Compound risk of high mortality following osteoporotic fracture and refracture in elderly women and men. J Bone Miner Res, 2013; 28: 2317–24
5. Guessous I, Cornuz J, Ruffieux C et al: Osteoporotic fracture risk in elderly women: Estimation with quantitative heel US and clinical risk factors. Radiology, 2008; 248: 179–84
6. Lee DO, Jee BC, Ku S et al: Relationships between the insulin-like growth factor I (IGF-I) receptor gene G3174A polymorphism, serum IGF-I levels, and bone mineral density in postmenopausal Korean women. J Bone Miner Metab, 2008; 26: 42–46
7. Ongphiphadhanakul B: Osteoporosis: The role of genetics and the environment. Forum Nutr, 2007; 60: 158–67
8. Zhou H, Mori S, Tanaka M et al: A missense single nucleotide polymorphism, V114I of the Werner syndrome gene, is associated with risk of osteoporosis and femoral fracture in the Japanese population. J Bone Miner Metab, 2015; 33: 694–700
9. Blumenfeld O, Williams FM, Valdes A et al: Association of interleukin-6 gene polymorphisms with hand osteoarthritis and hand osteoporosis. Cytokine, 2014; 69: 94–101
10. Jin HS, Kim J, Park S et al: Association of the I264T variant in the sulfide quinone reductase-like (SQRDL) gene with osteoporosis in Korean postmenopausal women. PLoS One, 2015;10: e135285
11. Dole NS, Kapinas K, Kessler CB et al: A single nucleotide polymorphism in osteonectin 3' untranslated region regulates bone volume and is targeted by miR-433. J Bone Miner Res, 2015; 30: 723–32
12. Xu GY, Qiu Y, Mao HJ: Common polymorphism in the *LRP5* gene may increase the risk of bone fracture and osteoporosis. Biomed Res Int, 2014; 2014: 290531
13. Kim MH, Choi YY, Han JM et al: Ameliorative effects of Schizandra chinensis on osteoporosis via activation of estrogen receptor (ER)-alpha/-beta. Food Funct, 2014; 5: 1594–601
14. Jeedigunta Y, Bhoomi RP, Kolla VK et al: Association of estrogen receptor alpha gene polymorphisms with BMD and their affect on estradiol levels in pre- and postmenopausal women in south Indian population from Andhra Pradesh. Clin Chim Acta, 2010; 411: 597–600
15. Mencej-Bedrac S, Prezelj J, Kocjan T et al: The combinations of polymorphisms in vitamin D receptor, osteoprotegerin and tumour necrosis factor superfamily member 11 genes are associated with bone mineral density. J Mol Endocrinol, 2008; 42: 239–47
16. Zintzaras E, Rodopoulou P, Koukoulis GN: BsmI, TaqI, ApaI and FokI polymorphisms in the vitamin D receptor (VDR) gene and the risk of osteoporosis: A meta-analysis. Dis Markers, 2006; 22: 317–26
17. Estrada K, Styrkarsdottir U, Evangelou E et al: Genome-wide meta-analysis identifies 56 bone mineral density *loci* and reveals 14 *loci* associated with risk of fracture. Nat Genet, 2012; 44: 491–501
18. Ozmen B, Kirmaz C, Aydin K et al: Influence of the selective oestrogen receptor modulator (raloxifene hydrochloride) on IL-6, TNF-alpha, TGF-beta1 and bone turnover markers in the treatment of postmenopausal osteoporosis. Eur Cytokine Netw, 2007; 18: 148–53
19. Georgescu C, Seck T, Diel I et al: Bone matrix insulin-like growth factor (IGF)-I, IGF-II and transforming growth factor (TGF)-beta1 levels in men and postmenopausal women with osteoporosis: Lack of association with circulating growth factors and bone mineral density. Rev Med Chir Soc Med Nat Iasi, 2004; 108: 281–86
20. Prestes AP, Marques FZ, Hutz MH et al: Tobacco smoking and the ADRA2A C-1291G polymorphism. J Neural Transm (Vienna), 2007; 114: 1503–6
21. Maestu J, Allik J, Merenakk L et al: Associations between an alpha 2A adrenergic receptor gene polymorphism and adolescent personality. Am J Med Genet B Neuropsychiatr Genet, 2008; 147B: 418–23
22. Park YM, Chung YC, Lee SH et al: Weight gain associated with the alpha2a-adrenergic receptor -1,291 C/G polymorphism and olanzapine treatment. Am J Med Genet B Neuropsychiatr Genet, 2006; 141B: 394–97
23. Mlakar V, Jurkovic Mlakar S, Zupan J et al: ADRA2A is involved in neuro-endocrine regulation of bone resorption. J Cell Mol Med, 2015; 19: 1520–29
24. Moran JM, Pedrera-Canal M, Rodriguez-Velasco FJ et al: Lack of association of vitamin D receptor BsmI gene polymorphism with bone mineral density in Spanish postmenopausal women. PeerJ, 2015; 3: e953
25. Zhang C, Ma J, Chen G et al: Evaluation of common variants in *CNR2* gene for bone mineral density and osteoporosis susceptibility in postmenopausal women of Han Chinese. Osteoporos Int, 2015; 26: 2803–10
26. Zhang L, Yin X, Wang J et al: Associations between VDR gene polymorphisms and osteoporosis risk and bone mineral density in postmenopausal women: A systematic review and meta-analysis. Sci Rep, 2018; 8: 981
27. Sun J, Zhang C, Xu L et al: The transforming growth factor-beta1 (TGF-beta1) gene polymorphisms (TGF-beta1 T869C and TGF-beta1 T29C) and susceptibility to postmenopausal osteoporosis: A meta-analysis. Medicine (Baltimore), 2015; 94: e461
28. Ling Y, Lin H, Aleteng Q et al: Cdx-2 polymorphism in Vitamin D Receptor gene was associated with serum 25-hydroxyvitamin D levels, bone mineral density and fracture in middle-aged and elderly Chinese women. Mol Cell Endocrinol, 2016; 427: 155–61
29. Horváth P, Balla B, Kósa JP et al: Strong effect of SNP rs4988300 of the *LRP5* gene on bone phenotype of Caucasian postmenopausal women. J Bone Miner Metab, 2016; 34: 79–85
30. Lin J, Yang Y, Fei Q et al: Validation of three tools for identifying painful new osteoporotic vertebral fractures in older Chinese men: Bone mineral density, Osteoporosis Self-Assessment Tool for Asians, and fracture risk assessment tool. Clin Interv Aging, 2016;11: 461–69

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31. Longo AB, Ward WE: PUFAs, bone mineral density, and fragility fracture: Findings from human studies. Adv Nutr, 2016; 7: 299–312
32. Vilaca T, Gossiel F, Eastell R: Bone turnover markers: use in fracture prediction. J Clin Densitom, 2017; 20: 346–52
33. Sousa CP, Dias IR, Lopez-Pena M et al: Bone turnover markers for early detection of fracture healing disturbances: A review of the scientific literature. An Acad Bras Cienc, 2015; 87: 1049–61
34. Ivaska KK, Gerdhem P, Åkesson K et al: Effect of fracture on bone turnover markers: A longitudinal study comparing marker levels before and after injury in 113 elderly women. J Bone Miner Res, 2007; 22: 1155–64
35. Kim JG, Lim KS, Ku S et al: Relations between interleukin-1, its receptor antagonist gene polymorphism, and bone mineral density in postmenopausal Korean women. J Bone Miner Metab, 2005; 24: 53–57
36. Alvarez L, Guanabens N, Peris P et al: [The clinical utility of biochemical markers of bone remodeling]. Med Clin (Barc), 1999; 112: 517–18 [in Spanish]

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]