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Original Article

BMP7 gene polymorphisms are not associated with bone mineral density or osteoporotic fractures in postmenopausal Chinese women

Li-hong GAO, Shan-shan LI, Chong SHAO, Wen-zhen FU, Yu-juan LIU, Jin-wei HE, Zhen-lin ZHANG

Metabolic Bone Diseases and Genetic Research Unit, Division of Osteoporosis and Bone Diseases, Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

Aim: A previous study shows that bone morphogenetic protein 7 (BMP7) gene polymorphisms are associated with bone mineral density (BMD) in 920 European Americans. To determine the association of BMP7 polymorphisms and BMD and osteoporotic fracture susceptibility, we performed a case-control association study in postmenopausal Chinese women with or without osteoporotic fracture.
Methods: A total of 3815 unrelated postmenopausal Chinese women (1238 with osteoporotic fracture and 2577 healthy controls) were recruited. BMDs of the lumbar spine 1–4 (L1–4) and proximal femur (including total hip and femoral neck) were measured using dual-energy X-ray absorptiometry. Eight tagging single nucleotide polymorphisms (SNPs) in BMP7 gene, including rs11086598, rs4811822, rs12481628, rs6025447, rs230205, rs17404303, rs162316 and rs6127980, were genotyped.
Results: Among the 8 SNPs, rs6025447 and rs230205 were associated with total hip BMD (P=0.013 and 0.045, respectively). However, the associations became statistically insignificant after adjusting for age, height and weight. The TGTG haplotype of BMP7 gene was associated with total hip BMD (P=0.032), even after adjusting for age, height and weight (P=0.048); but the association was insignificant after performing the Bonferroni multiple-significance-test correction. Moreover, the 8 SNPs and 9 haplotypes of BMP7 gene were not associated with L1–4 or femoral neck BMD or osteoporotic fracture.
Conclusion: This large-sample case-control association study suggests that the common genetic polymorphisms of BMP7 gene are not major contributors to variations in BMD or osteoporotic fracture in postmenopausal Chinese women.

Keywords: bone morphogenetic protein 7; gene polymorphisms; bone mineral density; osteoporotic fracture; postmenopausal Chinese women

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Introduction

Of all osteoporosis phenotypes, bone mineral density (BMD) is the gold standard for osteoporosis diagnosis as well as one of the best predictors of osteoporotic fractures[1]. Genetic factors play a significant role in the determination of BMD and osteoporosis risk[2, 3]. Recently, an increasing number of novel genetic loci have been identified as being associated with osteoporosis and/or osteoporotic fracture risk[4–6]. Bone morphogenetic protein 7 (BMP7), along with other BMPs, is a member of the transforming growth factor (TGF) family. BMPs participate in organ development, regeneration, and wound healing and have numerous, highly diverse biological functions[7]. BMPs are especially well studied in bone formation and fracture healing. Previous studies have found that BMPs can recruit stem cells to injured sites and induce osteoblast proliferation[8–10]. In addition, BMP7 inhibits osteoclast formation from monocyte precursor cells *in vitro*[11]. In recent years, recombinant BMPs, particularly BMP2 and BMP7, have been used therapeutically in patients with large bone defects or delayed or impaired fracture healing, based on the notion that locally applied BMPs promote bone repair[12]. The results of a study based on 920 European Americans from 374 Diabetes Heart Study families (762 with type 2 diabetes) indicated that *BMP7* gene polymorphisms were associated with several measures of BMD[13]. However, no systemic association study has been performed to investigate the relationship between *BMP7* polymorphisms and BMD or osteoporotic fractures in an Asian population. To identify the association of *BMP7* polymorphisms and BMD and/or osteoporotic fracture susceptibility, we performed this case-control association study in

*To whom correspondence should be addressed.
E-mail zzl2002@medmail.com.cn.
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postmenopausal Chinese women with or without osteoporotic fracture.

Materials and methods

Study population

This study was approved by the Ethics Committee of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital. A total of 3920 unrelated, independent, ambulatory postmenopausal women were recruited from community centers, outpatient clinics and healthy volunteers. Women who had been naturally postmenopausal for more than 1 year and were older than 50 years were eligible for the study. All participants underwent a physical examination and routine laboratory measurements. The study population consisted of 1278 postmenopausal women with osteoporotic fractures (OF group) and 2642 healthy women without fractures (control group)[14]. The subjects in the OF group had at least one osteoporotic fracture in the vertebra, hip or distal radius. The criteria for exclusion from this study were described in our previous study[14]. Briefly, we excluded subjects who were receiving treatment or had medical complications known to affect bone metabolism. Finally, a total of 3815 postmenopausal women (1238 with osteoporotic fracture and 2577 controls) were retained in the study for analysis. All participants were of Han ethnicity. All participants signed an informed consent form before inclusion.

BMD measurement

The BMD (g/cm^2) of the lumbar spine 1–4 (L1–L4), left femoral neck and total hip was measured by dual-energy X-ray absorptiometry (DXA) with Lunar Prodigy equipment (GE Lunar Corp, Madison, WI, USA). If an osteoporotic fracture of the left hip was noted, we measured the right femoral neck and the right total hip. If an osteoporotic fracture of one of the vertebrae (L1–L4) was observed, we excluded the BMD measurement of the osteoporotic vertebrae and used the BMD of the remaining vertebrae for analysis. The Lunar device was calibrated daily. Quality assurance scans were conducted by scanning an aluminum spine phantom according to the manufacturer's instructions. The coefficient of variability (CV) values of the DXA measurements of the lumbar spine, femoral neck, and total hip were 1.39%, 2.22%, and 0.70%, respectively[15–17]. All DXA scans were conducted by the same well-trained technologist throughout the study.

SNP selection and genotyping

Eight tagged *BMP7* SNPs (rs11086598, rs4811822, rs12481628, rs6025447, rs230205, rs17404303, rs162316, and rs6127980) were selected for evaluation based on data from HapMap (http://www.hapmap.org) and NCBI (http://www.ncbi.nlm.nih.gov/SNP/). The SNPs were selected based on the following criteria: (a) degree of heterozygosity [minor allele frequencies (MAFs)>0.05] and (b) tagged *BMP7* SNPs with r^2>0.8. To genotype the selected tagged SNPs (tagSNPs), genomic DNA was extracted from peripheral blood samples and purified using the QuickGene DNA whole blood kit L by Nucleic Acid Isolation System QuickGene-610L. SNPs were genotyped using the ABI PRISM SNaPshot multiplex kit (Applied Biosystems), Mx3000p real-time PCR system (Stratagene, La Jolla, CA, USA) and GeneMapper 4.1 (Applied Biosystems). Genotype frequencies were assessed for Hardy-Weinberg equilibrium (HWE) using the chi-squared test to detect genotyping errors.

Identification of osteoporotic fractures

The identification of osteoporotic fractures was performed as described previously[14]. Nontraumatic fractures were defined as resulting from a fall from standing height or less or as manifesting without any trauma[18]. Reports of incident fractures of the hip, vertebrae, or forearm after menopause were collected and confirmed. In addition, lateral X-rays of the spine covering T4–L5 of all the participants were performed at inclusion. The X-rays were reviewed by the radiologists who did not participate in the genotyping or subsequent statistical analyses. Vertebral fractures were classified by the Genant semiquantitative method[19, 20].

Statistical analysis

Every SNP was assessed for compliance with Hardy-Weinberg equilibrium using the χ^2 goodness-of-fit statistic. The level of linkage disequilibrium (LD) among *BMP7* SNPs was assessed based on the observed haplotype and allele frequencies using Haploview version 3.2[21]. Lewontin's D' and the LD coefficient r^2 were calculated for all pairs of biallelic loci. Haplotypes were constructed from the population genotype data using the test implemented in PLINK[22]. Normal data are presented as the mean±SD.

Quality-control filtering and allele, genotype, and haplotype association tests between the adjusted parameters and SNPs were conducted using the Wald test implemented in PLINK[22]. All data were adjusted according to age, height and weight covariates using a linear regression approach. Logistic regression was used to calculate the odds ratio (OR) for fracture risk. The presence or absence of fractures was computed within each group of homozygous wild-type, heterozygous, and homozygous variant genotypes for each SNP. The homozygous wild-type was selected as the most common homozygous genotype. Analysis of covariance (ANCOVA) was used to estimate the BMD of each region for various genotype groups after adjustment for covariates (age, height and weight). We adopted the most conservative method (Bonferroni multiple-significance-test correction) to address the problem of multiple comparisons. The threshold for replication significance was set at P<0.05. Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

General characteristics of the study population

The general characteristics of the 3815 postmenopausal women in the study are presented in Table 1. In the study, 1238 postmenopausal women with osteoporotic fractures and 2577 controls were included for the association analysis. Of the 1238 osteoporotic fracture patients, 699 (56.46%) had vertebral frac-

Table 1. General characteristics of participants in the entire case-control group. The data are presented as the mean±SD.

	Control group	Case group	*P* value
	n=2577	*n*=1238	
Age (year)	62.81±7.66	69.92±8.44	<0.01
Height (cm)	154.83±5.46	152.03±6.78	<0.01
Weight (kg)	57.48±8.44	55.61±9.35	<0.01
BMI (kg/m^2)	23.96±3.19	24.17±3.62	0.219
L1–L4 BMD (g/cm^2)	0.92±0.19	0.85±0.19	<0.01
Femoral neck BMD (g/cm^2)	0.74±0.12	0.67±0.11	<0.01
Total hip BMD (g/cm^2)	0.80±0.13	0.71±0.12	<0.01

BMI: body mass index.

tures, 337 (27.22%) had wrist fractures, and 202 (16.32%) had hip fractures.

Allele frequencies and haplotype structures

Genotype data from the 3815 subjects were used to calculate the allele frequencies and the MAFs of the 8 tagSNPs in our study. The results show that the MAFs of the 8 tagSNPs in the current study were similar to those found in Han Chinese in Beijing (Table 2). The genotype frequencies of all 8 SNPs did not deviate from Hardy-Weinberg equilibrium (P>0.05). We distinguished two blocks in the *BMP7* gene containing (1) rs4811822, rs12481628, rs6025447, and rs230205 and (2) rs162316 and rs6127980 (Figure 1A). Based on these polymorphisms, significant LD was observed across the gene, and we inferred the existence of 6 and 3 haplotypes in these two blocks, respectively (Figure 1B).

Associations of *BMP7* genotypes and haplotypes with BMD

We adjusted all variables using the significant covariates of age, height and weight. rs6025447 and rs230205 were associated with total hip BMD (P-values were 0.013 and 0.045, respectively). However, the significance of the association disappeared after adjusting for age, height and weight (Table 3). The TGTG haplotype of *BMP7* was significantly associated with total hip BMD (P=0.032), even after adjusting for age, height and weight (P=0.048, Table 3). However, no significant

Table 2. The 8 *BMP7* SNPs genotyped in this study.

SNP	Chr position	Functional change	Alleles	Test for HWE (*P* value)	MAF (this study)	MAF (HapMap-HCB)
rs11086598	55743803	3′_flanking	C>T	0.91	0.29	0.30
rs4811822	55778969	intron 2	C>T	0.32	0.21	0.29
rs12481628	55787622	intron 2	G>A	0.60	0.26	0.34
rs6025447	55790147	intron 2	C>T	0.64	0.32	0.33
rs230205	55791756	intron 2	G>A	0.28	0.32	0.40
rs17404303	55803687	intron 1	C>T	0.99	0.03	0.05
rs162316	55809452	intron 1	G>A	0.09	0.31	0.37
rs6127980	55823762	intron 1	G>A	0.06	0.21	0.17

HWE: Hardy-Weinberg equilibrium, MAF: minor allele frequency.

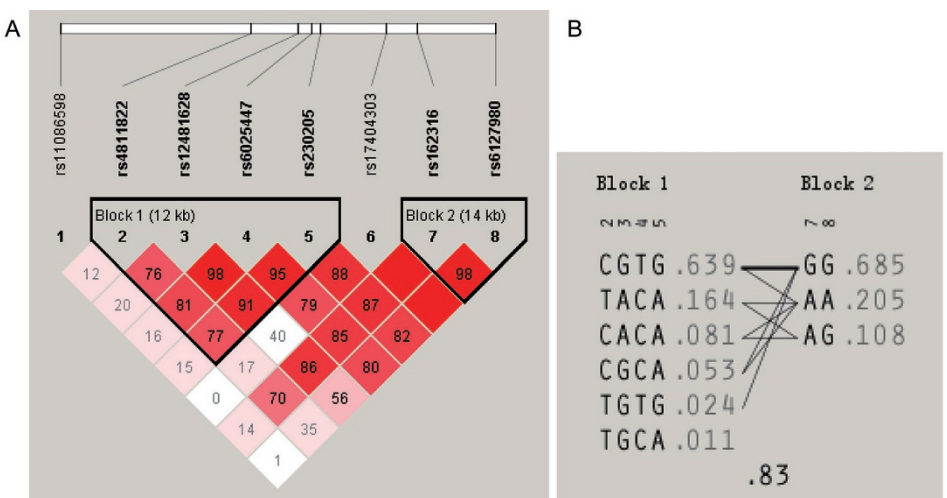

Figure 1. Linkage disequilibrium (LD) pattern for the *BMP7* gene. (A) LD plots for the *BMP7* gene. *D*′ values multiplied by 100 are presented as a number in the squares. (B) Six and three inferred haplotypes of the two blocks for the *BMP7* gene (frequency>1%).

Table 3. Associations between 8 SNPs, 9 haplotypes of *BMP7* and the BMD of total hip.

SNP	BETA	R^2	*P*	P^a	Haplotype	BETA	R^2	*P*	P^a
rs11086598	0.000	1.17×10^{-6}	0.953	0.696	TACA	-0.006	0.001	0.253	0.573
rs4811822	-0.001	1.12×10^{-5}	0.854	0.799	CACA	-0.008	0.000	0.257	0.076
rs12481628	-0.001	0.001	0.056	0.443	TGCA	0.010	0.002	0.598	0.596
rs6025447	-0.009	0.002	**0.013***	0.230	CGCA	-0.010	0.000	0.223	0.354
rs230205	-0.008	0.001	**0.045***	0.488	TGTG	0.028	0.000	**0.032***	**0.048***
rs17404303	-0.008	0.000	0.484	0.795	CGTG	0.007	0.000	0.079	0.170
rs162316	-0.005	0.000	0.195	0.916	AA	-0.003	0.000	0.429	0.513
rs6127980	-0.003	0.000	0.478	0.237	AG	-0.005	0.000	0.363	0.464
					GG	0.004	0.000	0.235	0.319

BETA: regression coefficient; R^2: squared regression coefficient (r); [a]: Adjusted for age, height and weight. **P*<0.05 are shown in bold.

association was found after performing the Bonferroni multiple-significance-test correction. No association was found between the 8 SNPs, 9 haplotypes of *BMP7* and femoral neck or L1–4 BMD using PLINK (Supplementary Table S1, S2).

Associations between *BMP7* genotypes and haplotypes and osteoporotic fractures

In the entire case-control group association analysis, no association was identified between the 8 SNPs or 9 haplotypes and the risk of osteoporotic fractures after adjusting for age, height and weight (Table 4, Supplementary Table S3). To further study the association of *BMP7* gene polymorphisms and osteoporotic fractures, the entire case group was divided into three subgroups based on wrist, vertebral or hip fractures. No significant differences in age, height, weight and BMI were detected between the three subgroups. Although no SNPs had significant allelic associations with hip, wrist or vertebral fractures, the GA genotype of rs12481628 [*P*=0.047, OR=0.745, 95% CI (0.557–0.996)], the CT genotype of rs6025447 [*P*=0.022, OR=0.715, 95% CI (0.537–0.952)] and the genotype GA of rs230205 [*P*=0.039, OR=0.740, 95% CI (0.556–0.985)] were significantly associated with osteoporotic wrist fractures. However, the significance disappeared after performing the Bonferroni multiple-significance-test correction (Table 5). No haplotypes had significant associations with hip, wrist or vertebral fractures (Supplementary Table S3).

Discussion

Osteoporosis and osteoporotic fractures, one of the most serious complications of osteoporosis, are major health threats for elderly individuals, especially for postmenopausal women. With the development of genetic testing technology, many candidate genes associated with BMD and osteoporosis or osteoporotic fractures have been identified[14, 23–25], thus promoting the exploration of the underlying genetic mechanisms and therapeutic targets for osteoporosis, osteoporotic fractures and other diseases affecting bone metabolism. To the best of our knowledge, this is the first large-scale case-control study to identify the association between *BMP7* gene polymorphisms and BMD and osteoporotic fracture in postmenopausal Chinese women, even in an Asian female population.

Based on the knowledge that BMP7 plays an important role in bone formation and fracture healing, we hypothesized that *BMP7* polymorphisms may serve as susceptibility factors for osteoporosis and/or osteoporotic fractures in postmenopausal women. However, neither *BMP7* genotype nor haplotype was correlated with BMD or osteoporotic fracture in postmenopausal Chinese women. The findings from our study were inconsistent with those from previous studies. In the study on the association of *BMP7* SNPs with BMD measured

Table 4. The minor allele ORs and 95% CIs of 8 SNPs of BMP7 in the entire case–control group and three site–specific fracture subgroups.

SNP	Entire case–control group OR (95% CI)	*P*	Wrist fracture OR (95% CI)	*P*	Vertebra fracture OR (95% CI)	*P*	Hip fracture OR (95% CI)	*P*
rs11086598	1.114 (0.979–1.268)	0.100	1.082 (0.884–1.324)	0.446	1.087 (0.931–1.269)	0.290	1.043 (0.800–1.360)	0.758
rs4811822	1.100 (0.955–1.268)	0.187	0.854 (0.676–1.079)	0.186	1.136 (0.959–1.345)	0.140	1.184 (0.899–1.576)	0.248
rs12481628	1.056 (0.926–1.203)	0.417	0.927 (0.751–1.144)	0.480	1.109 (0.949–1.296)	0.194	1.197 (0.920–1.559)	0.181
rs6025447	1.030 (0.911–1.165)	0.639	0.860 (0.705–1.048)	0.136	1.091 (0.942–1.264)	0.246	1.041 (0.807–1.342)	0.757
rs230205	1.048 (0.927–1.184)	0.459	0.788 (0.604–1.030)	0.081	1.018 (0.833–1.243)	0.865	0.933 (0.658–1.323)	0.697
rs17404303	1.227 (0.866–1.740)	0.251	0.928 (0.521–1.652)	0.799	1.107 (0.730–1.679)	0.633	1.200 (0.604–2.386)	0.603
rs162316	1.008 (0.891–1.140)	0.899	0.874 (0.717–1.065)	0.182	1.037 (0.896–1.202)	0.625	1.211 (0.945–1.552)	0.131
rs6127980	1.048 (0.912–1.205)	0.509	0.906 (0.722–1.137)	0.394	1.066 (0.903–1.259)	0.449	1.180 (0.892–1.562)	0.246

OR: odds ratio; 95% CI: 95% confidence interval.

Table 5. The genotypic ORs and 95% CIs of 8 SNPs of BMP7 in the entire case–control group and three site–specific fracture subgroups.

SNP		Entire case–control group		Wrist fracture		Vertebra fracture		Hip fracture	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
rs11086598	CC								
	CT	1.147 (0.962–1.367)	0.127	1.28 (0.965–1.697)	0.870	1.112 (0.892–1.387)	0.345	1.002 (0.688–1.459)	0.991
	TT	1.202 (0.885–1.633)	0.239	0.969 (0.568–1.653)	0.907	1.085 (0.737–1.599)	0.679	1.229 (0.665–2.271)	0.511
rs4811822	CC								
	CT	1.076 (0.902–1.284)	0.414	0.822 (0.612–1.104)	0.192	1.181 (0.947–1.472)	0.140	1.032 (0.704–1.511)	0.873
	TT	1.276 (0.857–1.900)	0.229	0.994 (0.513–1.926)	0.986	1.156 (0.694–1.927)	0.577	1.868 (0.913–3.818)	0.087
rs12481628	GG								
	GA	0.957 (0.804–1.140)	0.625	0.745 (0.557–0.996)	**0.047***	1.015 (0.815–1.265)	0.891	0.944 (0.646–1.379)	0.766
	AA	1.279 (0.933–1.753)	0.126	1.243 (0.760–2.031)	0.386	1.271 (0.855–1.889)	0.235	1.749 (0.971–3.150)	0.063
rs6025447	CC								
	CT	0.893 (0.749–1.065)	0.209	0.715 (0.537–0.952)	**0.022***	0.980 (0.785–1.223)	0.859	0.682 (0.462–1.006)	0.054
	TT	1.194 (0.912–1.562)	0.198	0.904 (0.576–1.411)	0.657	1.211 (0.862–1.700)	0.270	1.338 (0.800–2.2399)	0.267
rs230205	GG								
	GA	0.961 (0.806–1.146)	0.660	0.740 (0.556–0.985)	**0.039***	1.011 (0.810–1.261)	0.925	0.907 (0.620–1.327)	0.617
	AA	1.170 (0.892–1.534)	0.258	0.874 (0.557–1.371)	0.557	1.185 (0.842–1.667)	0.331	1.294 (0.752–2.227)	0.352
rs17404303	CC								
	CT	1.196 (0.835–1.713)	0.328	1.041 (0.568–1.908)	0.896	1.099 (0.698–1.730)	0.684	1.275 (0.616–2.640)	0.513
	TT	1.356 (0.064–28.886)			1.000		1.000		1.000
rs162316	GG								
	GA	0.934 (0.783–1.114)	0.447	0.785 (0.590–1.045)	0.097	0.979 (0.785–1.222)	0.853	0.920 (0.625–1.355)	0.674
	AA	1.084 (0.824–1.426)	0.563	0.851 (0.593–1.343)	0.487	1.074 (0.760–1.518)	0.686	1.514 (0.901–2.544)	0.117
rs6127980	GG								
	GA	1.097 (0.916–1.314)	0.314	0.966 (0.718–1.298)	0.817	1.188 (0.941–1.478)	0.132	0.995 (0.671–1.476)	0.982
	AA	0.995 (0.681–1.454)	0.980	0.768 (0.398–1.482)	0.431	0.881 (0.542–1.475)	0.618	1.674 (0.869–3.227)	0.124

OR: odds ratio; 95% CI: 95% confidence interval. *$P<0.05$ are in bold.

using DXA (lumbar spine, hip, and distal radius) and quantitative CT (QCT; thoracic and lumbar spine) in 920 European Americans from 374 Diabetes Heart Study families (762 with type 2 diabetes), *BMP7* SNP rs17404303 was associated with thoracic spine-QCT BMD, lumbar spine-QCT BMD, distal radius-DXA BMD and a trend for hip-DXA BMD, whereas minor allele homozygotes at rs17404303 had a significantly decreased median BMD[13]. However, no association was observed between the polymorphism rs17404303 of *BMP7* and BMD in postmenopausal women in the current study. The discrepancy may be due to type 2 diabetes. Subjects with type 2 diabetes have increased hip and spine BMD compared with subjects without diabetes[26]. In addition, the following factors should be taken into consideration. First, genetic factors exert a strong and perhaps a predominant influence on peak bone mass; however, physiological, environmental and modifiable lifestyle factors, such as adequate and appropriate nutrition and body weight, exposure to sex hormones at puberty and physical activity, can also play a significant role. Second, BMD assessed by conventional DXA measures the total bone mineral content in a projected area (integral areal BMD) and cannot directly measure other skeletal features that may also contribute to bone strength, such as the relative amounts of cortical and trabecular bone. Quantitative computed tomography (QCT) can provide a direct measure of cortical and trabecular volumetric BMD, both of which may contribute to bone strength and fracture risk[27]. In addition, individual genetic factors contributing to BMD variation may differ between women and men, between skeletal sites, and between trabecular and cortical bone[28]. Volumetric BMD (vBMD) for both compartments is heritable, with heritability estimates of 17% to 42% for cortical vBMD and 59% to 73% for trabecular vBMD[29–31]. In a study aiming to investigate the candidate gene of femoral neck trabecular and cortical vBMD in older men by genotyping 4608 tagging and potentially functional SNPs in 383 bone metabolism candidate genes in 822 Caucasian men aged 65 years or older from the Osteoporotic Fractures in Men Study (MrOS), the results indicated that rs6127983 of BMP7 was robustly associated with trabecular vBMD[32].

Osteoporotic fracture is an outcome of low-trauma to bone of compromised strength, and its incidence is increased by various risk factors. Candidate gene variants for osteoporotic fracture are not simply the same as those for low BMD[33, 34]. Studies demonstrated a heritability of 50%–80% for BMD, but fracture heritability has been estimated to be less than 50%[35]. To the best of our knowledge, there are no findings suggesting that *BMP7* gene polymorphisms are associated with osteoporotic fractures in postmenopausal women. However, we should realize that the risk of osteoporotic fracture is complex and regulated by both environmental and genetic factors. Fracture risk is associated with a history of falls; low physical

function, such as slow gait speed and decreased quadriceps strength; impaired cognition; poor vision; and the presence of environmental hazards[36]. Although the measurement of BMD has been one of the best methods to determine the risk of osteoporotic fracture, a meta-analysis of the predictive ability of the measurement for hip fracture reported a false positive rate of 15% and a detection rate of only 50%[37]. Kannus and colleagues found that susceptibility to osteoporotic fractures in elderly Finns is not strongly influenced by genetic factors, especially in elderly women[38]. The results of many studies indicate that clinical risk factors related to risk of falls also serve as important predictors of fracture[39–41].

One of the strengths of the present study was that a large number of individuals with the same fracture type were recruited, and a direct genetic evaluation of osteoporotic fracture using a case-control method was performed. Another strength was that the fracture data obtained for the case group were verified by hospital radiographs rather than comprising a collection of self-reported fractures. Our study also had several potential limitations. First, we focused on postmenopausal Chinese women, and our findings may not be generalizable to other populations. As peak bone mass is an important factor in determining long-term fracture risk, additional genotyping in younger women, ethnically diverse populations, and men will be necessary to further confirm our findings. Second, we cannot assess the impact that rare variants may have on BMD or osteoporotic fracture in our study because we restricted our analysis to tagSNPs with an MAF>5%. Future studies may need to consider other types of polymorphisms, such as insertion-deletions, copy-number variants, and less common SNPs (<5% MAF), as well as interactions between genes and between genes and environmental factors to better account for the phenotypic variation in BMD. Third, further study of the factors that can predict bone mass, bone quality or osteoporotic fracture assessed by techniques other than DXA is needed to clarify the association between *BMP7* gene polymorphisms and osteoporosis and fracture in postmenopausal women. Additionally, a number of factors that affect BMD, such as menopausal age, menopausal time and life style, were not considered in the analysis. Finally, fracture risk involves a combination of bone-dependent and bone-independent factors. Bone-independent factors include muscle function and cognition, which also contribute to falls leading to fractures. Therefore, a comprehensive assessment of bone-dependent and bone-independent factors, such as fall frequency, should be included.

In conclusion, *BMP7* SNPs were not associated with BMD or osteoporotic fracture in postmenopausal Chinese women in this large-scale investigation. Although additional studies are needed to confirm and extend our findings, the current analysis suggests that the common genetic polymorphisms of the *BMP7* gene are not major contributors to variations in BMD or osteoporotic fractures in postmenopausal Chinese women.

Acknowledgements

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Author contribution

Zhen-lin ZHANG designed the study and revised the manuscript; Li-hong GAO, Wen-zhen FU, Yu-juan LIU, and Jin-wei HE performed the study; Li-hong GAO analyzed the data and wrote the paper; Shan-shan LI and Chong SHAO provided invaluable suggestions for the data analysis.

Supplementary information

Supplementary information is available at the website of Acta Pharmacologica Sinica.

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