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Are bone mineral density loci associated with hip osteoporotic fractures? A validation study on previously reported genome-wide association loci in a Chinese population

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ABSTRACT. Osteoporosis is a heritable disease characterized mainly by low bone mineral density (BMD) and/or osteoporotic fractures (OF). Most genome-wide association studies on osteoporosis have focused on BMD, whereas little effort has been expended to identify genetic variants directly linked to OF. To determine whether BMD-loci are also associated with OF risk, we performed a validation study to examine 23 BMD-loci reported by recent genome-wide association studies for association with

hip OF risk. Our sample consisted of 700 elderly Chinese Han subjects, 350 with hip OF and 350 healthy matched controls. We identified four BMD-loci that were significantly associated with hip OF in this Chinese population, including 7q21 (*FLJ42280*, P = 1.17 × 10^{-4} for rs4729260; P = 0.008 for rs7781370), 6p21 (*MHC*, P = 0.004 for rs3130340), 13q14 (*TNFSF11*, P = 0.012 for rs9533090; P = 0.018 for rs9594759; P = 0.020 for rs9594738; P = 0.044 for rs9594751), and 18q21 (*TNFRSF11A*, P = 0.015 for rs884205). The SNP rs4729260 at 7q21 remained significantly associated, even after conservative Bonferroni's correction. Our results further highlight the importance of these loci in the pathogenesis of osteoporosis, and demonstrate that it is feasible and useful to use OF as the direct phenotype to conduct genetic studies, to enhance our understanding of the genetic architecture of osteoporosis.

Key words: Osteoporotic fractures; Genome-wide association studies; BMD; SNP

INTRODUCTION

Osteoporosis is a serious public health problem, which is characterized by reduced bone mineral density (BMD) and increased risk of low-trauma osteoporotic fractures (OF) (Melton, 2003). Hip fractures are the most common and severe type of OF, and directly associated with high morbidity and mortality, as well as tremendous health care costs (Cooper et al., 1992; Cummings and Melton, 2002). Due to an aging population, the incidence of hip OF is increasing greatly not only in developed countries, but also in developing countries (Lau et al., 1999, 2001). One third of the world's hip OF now occur in Asia, mostly in China, and this rate will rise to 45% by the year 2050 (Gullberg et al., 1997), with the number being roughly 3.2 million (Cooper et al., 1992).

Genetic factors play a significant role in osteoporosis. Recently, genome-wide association studies (GWAS) have become a major strategy for genetic dissection of complex human diseases/traits. Through this strategy, multiple novel genetic loci have been successfully identified for osteoporosis (Richards et al., 2008; Styrkarsdottir et al., 2008, 2009; Rivadeneira et al., 2009; Guo et al., 2010b). Most of these GWAS have been confined to using the surrogate phenotype BMD, since BMD has been widely accepted as the best predictor of OF (Johnell et al., 2005; Kanis et al., 2007). A successful example is that, deCODE Genetics (Styrkarsdottir et al., 2008, 2009) and the GEFOS Consortium (Richards et al., 2008; Rivadeneira et al., 2009) have reported 23 genomic loci that are associated with BMD at the genome-wide significance level in European populations. A follow-up replication study was recently performed by Styrkarsdottir et al. (2010), who replicated 14 of these 23 loci, which are also associated with BMD in the East-Asian population (two Chinese and one Korean samples). However, genetic factors underlying the BMD variations and OF risk overlap, to some extent but not all the same (Deng et al., 2002). We wondered if the BMD-related genetic variants are also associated with OF. OF is the clinically relevant endpoint phenotype of osteoporosis, and the ultimate goal of genetic studies of osteoporosis is to identify genes responsible for OF risk. Therefore, it is necessary and useful to conduct genetic studies of OF *per se*, which may help

us classify factors that counterbalance genetic effects of BMD, and enhance our understanding of the pathogenesis of osteoporosis.

Therefore, the aim of this study was to investigate if the BMD-related genetic variants are also associated with OF risk in a Chinese population. The markers we tested focused on the GWAS BMD loci reported by deCODE Genetics and the GEFOS Consortium (Richards et al., 2008; Rivadeneira et al., 2009; Styrkarsdottir et al., 2008, 2009, 2010).

MATERIAL AND METHODS

Study subjects

The study was approved by the local institutional review boards of the Xi'an Jiaotong University. After signing an informed consent, all subjects were assisted in completing a structured questionnaire including anthropometric variables, lifestyles, and medical history.

The Chinese OF sample consisted of 700 elderly Chinese Han subjects, 350 with osteoporotic hip fractures and 350 elderly healthy controls (see Table 1 for basic characteristics). Since fractures at different skeletal sites may have different underlying pathological mechanisms, we focused exclusively on hip fractures in order to minimize potential clinical and genetic heterogeneity of the study phenotype. All subjects were unrelated northern Chinese Han adults living in the city of Xi'an and its neighboring areas. Inclusion and exclusion criteria for cases have been detailed in our earlier publication (Guo et al., 2010a). These are briefly described as follows: i) age <80 years and onset age of hip OF >55 years, where all female subjects were postmenopausal women; ii) minimal or no trauma fractures, usually due to falls from standing height or less; iii) fracture at femoral neck or inter-trochanter regions; iv) fracture was identified/confirmed through diagnosis by orthopedic surgeons/radiologists according to radiological reports and X-rays. Patients with pathological fractures and high-impact fractures (such as due to motor vehicle accidents) were excluded.

Healthy control subjects were selected from our established large database as a ratio of 1:1 to cases. They were geography-matched to the cases. Inclusion criteria for controls were: i) age at examination >55 years, and without any fracture history, where oldest subjects were preferred; ii) subjects with chronic diseases and conditions that might potentially affect bone mass, structure, or metabolism were excluded. The exclusion will ensure that controls are less likely to suffer OF during the remainder of their life compared with general populations.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. SNP genotyping was performed using the Affymetrix Human Mapping 500K array set (Affymetrix, Santa Clara, CA, USA), which had been completed in our previous study (Guo et al., 2010a). The experimental procedure was followed by the Affymetrix protocol and the quality control standards. SNPs used in this study satisfied the following criteria: 1) genotyping call rate >95%; 2) not deviating from Hardy-Weinberg equilibrium (HWE; $P > 0.0001$); 3) minor allele frequency (MAF) >0.01. In addition, since our study aimed to investigate if the BMD-related loci previously reported by GWAS are also associated with OF (Richards et al., 2008; Rivadeneira et al., 2009; Styrkarsdottir et al., 2008, 2009, 2010),

for those reported SNPs, which were missing in our Affymetrix 500K arrays, we imputed the genotypes using the IMPUTE program (Marchini et al., 2007) to facilitate comparison of associations at the same SNPs. To ensure the reliability of the imputation, all of those imputed SNPs reached a calling threshold of 0.90, i.e., a 90% probability that an imputed genotype is true. In total, 50 SNPs from 22 loci were included for subsequent association analyses (Supplementary Table 1).

Statistical analyses

Before the association test, principal component analysis implemented in EIGENSTRAT (Price et al., 2006) was used to correct for potential population stratification that may lead to spurious association results for the OF sample. SNPTEST (Marchini et al., 2007) was used to test for associations between all the SNPs and OF risk. The covariates included age, gender, height, weight, and the first 10 principal components emerging from the EIGENSTRAT analyses. A raw P value of <0.05 in our study was considered to be nominally significant. Bonferroni's correction was used to account for multiple comparisons. The significance threshold was set at a P value of less than 0.001 (0.05/50 SNPs that were included in the association analyses).

RESULTS

The basic characteristics of the study subjects are presented in Table 1. The previously reported 23 BMD-loci identified by GWAS in European populations included 1p36 (*ZBTB40*), 1p31 (*GPR177*), 2p21 (*SPTBN1*), 3p22 (*CTNNB1*), 4q22 (*MEPE*), 5q14 (*MEF2C*), 6p21 (*MHC*), 6q25 (*ESR1*), 7p14 (*STARD3NL*), 7q21 (*FLJ42280*), 8q24 (*TNFRSR11B*), 11p15 (*SOX6*), 11p13 (*DCDC5*), 11p11 (*ARHGAP1*), 11q13 (*LRP5*), 12q13 (*SP7*), 13q14 (*TNFSF11*), 14q32 (*MARK3*), 16q24 (*FOXL1*), 17q21 (*SOST*), 17q21 (*HDAC5*), 17q12 (*CRHR1*), and 18q21 (*TNFRSF11A*) (Richards et al., 2008; Rivadeneira et al., 2009; Styrkarsdottir et al., 2008, 2009). Fourteen of these 23 loci were further reported to be associated with hip BMD in East-Asian populations (Chinese and Korean), including 1p36, 1p31, 3p22, 4q22, 5q14, 6q25, 7q21, 8q24, 11p15, 11q13, 13q14, 16q24, and 17q21 (Styrkarsdottir et al., 2010). In this study, we aimed to examine all these BMD-loci for association with hip OF. Since an SNP (rs9303521) from 17q12 failed imputation of genotype, 50 SNPs from 22 loci were included for association analyses. The association results for all SNPs tested are shown in Supplementary Table 1. Eight SNPs from four BMD-loci were identified to be nominally significantly associated with hip OF in this study ($P < 0.05$), including 6p21, 7q21, 13q14, and 18q21, which are summarized in Table 2. After applying Bonferroni's correction for multiple testing, a single SNP, rs4729260, remained significant ($P < 0.001$).

Table 1. The basic characteristics of the study subjects.

Parameter	Cases	Controls
Number	350	350
Age (years)	69.35 (7.41)	69.54 (6.09)
Weight (kg)	59.15 (12.05)	59.61 (10.84)
Height (cm)	162.84 (8.31)	159.41 (9.20)
Male/Female	124/226	173/177

Data are reported as means (standard deviation).

Table 2. Major association results between bone mineral density loci and hip osteoporotic fracture (P < 0.05).

Locus	Nearest gene	SNP	Position	Allele[a]	MAF cases	MAF controls	P value	OR (95%CI)
7q21	*FLJ42280*	rs4729260	95955854	G/C	0.155	0.085	1.17E-4	1.98 (1.39-2.80)
		rs7781370	95971467	T/C	0.154	0.102	0.008	1.59 (1.13-2.24)
6p21	*MHC*	rs3130340	32352605	C/T	0.158	0.218	0.004	1.48 (1.13-1.95)
13q14	*TNFSF11*	rs9533090	41849449	T/C	0.065	0.101	0.012	0.62 (0.42-0.91)
		rs9594759	41930593	T/C	0.183	0.233	0.018	0.74 (0.57-0.96)
		rs9594738	41850145	T/C	0.068	0.102	0.020	0.64 (0.44-0.94)
		rs9594751	41895267	T/C	0.039	0.062	0.044	0.61 (0.37-1.00)
18q21	*TNFRSF11A*	rs884205	58205837	A/C	0.036	0.084	0.015	2.47 (1.16-5.25)

MAF = minor allele frequency; OR = odds ratio; CI = confidence interval. [a]The former allele represents the minor allele.

The most significant SNP, rs4729260 at 7q21 (*FLJ42280*), achieved a P value of 1.17 × 10^{-4} for association with hip OF. The minor allele G of rs4729260 was associated with an increased risk of hip OF, with the odds ratio (OR) estimated to be 1.98 (95% confidence interval (CI) = 1.39-2.80). This was consistent with its association with lower hip BMD values in both European and East-Asian populations (Rivadeneira et al., 2009; Styrkarsdottir et al., 2010) (Table 3). Another SNP, rs7781370, which is in pairwise linkage disequilibrium (LD, r^2 = 0.78 in Chinese) with rs4729260, was also associated with increased risk of hip OF (P = 0.008). The OR was 1.59 (95%CI = 1.13-2.24) for minor allele T of rs7781370. This SNP was also reported to be associated with lower hip BMD values in both European and East-Asian populations (Rivadeneira et al., 2009; Styrkarsdottir et al., 2010).

Table 3. Difference in effect on hip bone mineral density (BMD) and osteoporotic fracture (OF) for European, East-Asian, and Chinese populations.

Locus	SNP	A1/A2	Hip BMD (Europe)[a]			Hip BMD (Asia)[b]			Hip OF (China)		
			Freq	P value	Effect	Freq	P value	Effect	Freq	P value	OR (95%CI)
7q21	rs4729260	G/C	0.20	5.4E-11	-0.09	0.134	3.8E-4	-0.08	0.120	1.17E-4	1.98 (1.39-2.80)
	rs7781370	T/C	0.340	2.9E-11	-0.08	0.132	2.5E-4	-0.08	0.129	0.008	1.59 (1.13-2.24)
6p21	rs3130340	C/T	0.205	0.0065	-0.05	0.240	0.07	-0.03	0.189	0.004	1.48 (1.13-1.95)
13q14	rs9533090	T/C	0.500	6.0E-4	-0.04	0.078	0.21	-0.02	0.083	0.012	0.62 (0.42-0.91)
	rs9594759	T/C	0.622	2.1E-6	-0.07	0.234	0.86	0.02	0.208	0.018	0.74 (0.57-0.96)
	rs9594738	T/C	0.568	1.9E-8	-0.10	0.086	0.065	-0.05	0.086	0.020	0.64 (0.44-0.94)
	rs9594751	T/C	0.265	2.1E-5	-0.07	0.065	0.18	-0.03	0.051	0.044	0.61 (0.37-1.00)
18q21	rs884205	A/C	0.270	0.005	-0.04	0.210	0.24	-0.01	0.061	0.015	2.47 (1.16-5.25)

Freq = frequency is shown for allele A1; OR = odds ratio; CI = confidence interval. [a]The data for hip BMD in Europe were from Styrkarsdottir et al. (2008) and Rivadeneira et al. (2009). [b]The data for hip BMD in Asia were from Styrkarsdottir et al. (2010).

The SNP rs3130340-C at 6p21 (*MHC*) and SNP rs884205-A at 18q21 (*TNFRSF11A*) were associated with an increased risk of hip OF (rs3130340: P = 0.004; rs884205: P = 0.015), and the ORs were estimated to be 1.48 (95%CI = 1.13-1.95) and 2.47 (95%CI = 1.16-5.25), respectively. These two SNPs were reported to be only associated with reduced hip and spine BMD values in European populations (Styrkarsdottir et al., 2008), but not in East-Asian populations (Styrkarsdottir et al., 2010) (Table 3).

Four SNPs at 13q14 (*TNFSF11*) were found to be associated with hip OF, including rs9533090-T (P = 0.012), rs9594759-T (P = 0.018), rs9594738-T (P = 0.020), and rs9594751-T (P = 0.044). The minor allele T of these four SNPs had a protective effect from hip OF (OR < 1,

Table 2) in our study. However, the effects of these four SNPs were totally different in Europeans, showing associations with lower hip BMD values (Styrkarsdottir et al., 2008, 2009). None of these four SNPs showed significant results in East-Asians (Styrkarsdottir et al., 2010) (Table 3).

DISCUSSION

In this study, we performed a validation analysis to investigate whether the BMD-loci reported by previous GWAS are also associated with hip OF risk in a Chinese population. We identified four loci significantly associated with hip OF, including 7q21, 6p21, 13q14, and 18q21.

The effects of 7q21 on BMD and OF were very consistent. However, we noticed that, in the East-Asian study (Styrkarsdottir et al., 2010), a significant signal of 7q21 on BMD was not detected when analyzing random BMD samples, whereas the effect was demonstrated when analyzing an extreme BMD sample. It may indicate that when true variants exist, using extreme BMD or OF as the studied phenotype could increase the statistical power to detect association signals.

For 6q21, 13q14, and 18q21, no significant signal was found in East-Asian populations (Styrkarsdottir et al., 2010), which was in contradiction with our results. One possible interpretation of this different effect would be that BMD is not the only risk factor for OF; other risk factors also contribute to the risk of OF (Marshall et al., 1996; Hazenberg et al., 2007). Therefore, it is not only necessary but also feasible and efficient to use OF as the direct phenotype to conduct genetic studies, in conjunction with other proximal phenotypes (e.g., BMD), aiming to expedite the genetic dissection of osteoporosis.

The results for other BMD-loci on OF were inconclusive, which may reflect the true differences in pathologic characteristics between BMD and OF. However, it may also be due to the lack of power in our study of the relatively small hip OF samples compared to the large BMD samples. In addition, a potential limitation of our study is that we could not test for associations with hip OF in European populations to compare the different effects of these loci more thoroughly. Follow-up studies performed with multiple and large sample sets in multiple populations are needed to validate our results and explore the generality of our findings.

The statistical power of our study was estimated by using the Genetic Power Calculator program (http://pngu.mgh.harvard.edu/~purcell/gpc/cc2.html). We set the population prevalence of hip OF to be 5%, which is conservatively compatible with epidemiology data (Melton, 2000; Siris, 2006). Assuming that a marker is in strong LD (D' = 0.9) with a functional mutation and that the risk allele has a minor frequency of 0.15, under the conservative significance level of P = 0.01, our sample can achieve >75% statistical power to detect a genetic variant individually incurring a relative risk of OF as low as 1.5 under additive effect.

It is worth emphasizing that all the subjects in our sample came from the same Chinese Han ethnicity and the same geographical area, and that all the case subjects experienced the same type of low-impact hip OF. The homogeneity of our sample minimized spurious association results due to phenotypic variation or other factors caused by population stratification.

In summary, our results further highlight the importance of these BMD-loci in the pathogenesis of osteoporosis. Future studies with larger sample size are warranted to identify additional loci associated not only with BMD but also with risk of OF, the ultimate clinical outcome of osteoporosis.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Association results for hip OF for all the SNPs tested in this study.

Locus	Nearest gene	SNP	Position	Allele[a]	MAF cases	MAF controls	P value	OR (95%CI)
1p36	*ZBTB40*	rs7524102	22571034	G/A	0.191	0.213	0.316	0.87 (0.67-1.14)
		rs6696981	22575445	T/G	0.190	0.209	0.383	0.89 (0.68-1.16)
		rs6426749	22584060	C/G	0.186	0.206	0.352	1.14 (0.87-1.49)
		rs7543680	22603856	A/G	0.236	0.243	0.754	1.04 (0.81-1.33)
1p31	*GPR177*	rs2566755	68407978	C/T	0.213	0.225	0.569	1.07 (0.83-1.38)
2p21	*SPTBN1*	rs11898505	54538061	A/G	0.059	0.054	0.776	0.93 (0.55-1.57)
3p22	*CTNNB1*	rs10490823	41098739	T/C	0.262	0.294	0.197	0.85 (0.67-1.08)
		rs87938	41112676	G/A	0.375	0.386	0.707	0.96 (0.77-1.19)
4q22	*MEPE*	rs1471403	88994267	T/C	0.337	0.338	0.969	0.99 (0.79-1.24)
5q14	*MEF2C*	rs1366594	88411817	A/C	0.375	0.383	0.795	1.04 (0.79-1.35)
6p21	*MHC*	rs3130340	32352605	C/T	0.158	0.218	0.004	1.48 (1.13-1.95)
6q25	*ESR1*	rs9479055	151889660	A/C	0.236	0.220	0.482	0.91 (0.71-1.18)
		rs9478223	151941931	C/T	0.050	0.051	0.885	1.04 (0.63-1.71)
		rs4870044	151943102	C/T	0.195	0.184	0.625	0.93 (0.70-1.23)
		rs1038304	151974868	G/A	0.467	0.506	0.149	0.86 (0.69-1.06)
		rs6929137	151978370	A/G	0.307	0.343	0.173	1.18 (0.93-1.49)
		rs7751941	151988351	A/G	0.022	0.029	0.409	1.32 (0.67-2.61)
		rs6900157	151995820	C/T	0.343	0.378	0.170	1.17 (0.94-1.45)
		rs2941740	152051331	G/A	0.178	0.148	0.152	1.23 (0.93-1.64)
		rs1999805	152110057	A/G	0.306	0.310	0.898	1.02 (0.81-1.28)
		rs2504063	152132400	G/A	0.226	0.204	0.388	1.13 (0.86-1.49)
7p14	*STARD3NL*	rs1524058	38102802	T/C	0.468	0.439	0.284	1.12 (0.91-1.39)
7q21	*FLJ42280*	rs4729260	95955854	G/C	0.155	0.085	1.17E-4	1.98 (1.39-2.80)
		rs7781370	95971467	T/C	0.154	0.102	0.008	1.59 (1.13-2.24)
8q24	*TNFRSF11B*	rs4355801	119993054	G/A	0.278	0.295	0.483	0.92 (0.73-1.17)
		rs2062377	120076601	T/A	0.273	0.295	0.348	0.89 (0.71-1.13)
		rs6469792	120077552	T/C	0.411	0.430	0.470	0.92 (0.75-1.15)
		rs6469804	120114010	G/A	0.206	0.231	0.243	0.86 (0.67-1.11)
		rs6993813	120121419	T/C	0.346	0.369	0.367	0.91 (0.73-1.13)
11p15	*SOX6*	rs7117858	15651038	G/A	0.197	0.181	0.437	1.11 (0.89-1.39)
11p13	*DCDC5*	rs16921914	31167347	A/G	0.367	0.392	0.358	1.11 (0.89-1.40)
11p11	*ARHGAP1*	rs7932354	46678797	C/T	0.322	0.333	0.665	1.05 (0.84-1.32)
11q13	*LRP5*	rs599083	67948922	G/T	0.259	0.244	0.532	0.93 (0.72-1.19)
		rs3736228	67957871	T/C	0.194	0.170	0.211	1.17 (0.89-1.55)
12q13	*SP7*	rs2016266	52014222	G/A	0.193	0.193	0.991	1.00 (0.76-1.33)
13q14	*TNFSF11*	rs7992970	41843463	G/A	0.323	0.334	0.648	0.95 (0.76-1.19)
		rs9533090	41849449	T/C	0.065	0.101	0.012	0.62 (0.42-0.91)
		rs9594738	41850145	T/C	0.068	0.102	0.020	0.64 (0.44-0.94)
		rs9533093	41859597	T/C	0.406	0.421	0.575	0.94 (0.76-1.17)
		rs10507508	41867782	G/A	0.115	0.138	0.195	0.81 (0.59-1.12)
		rs9594751	41895267	T/C	0.039	0.062	0.044	0.61 (0.37-1.00)
		rs9594759	41930593	T/C	0.183	0.233	0.018	0.74 (0.57-0.96)
14q32	*MARK3*	rs2010281	102932075	A/G	0.140	0.137	0.877	0.98 (0.72-1.32)
16q24	*FOXL1*	rs10048146	85268161	G/A	0.221	0.247	0.407	0.86 (0.61-1.22)
17q21	*SOST*	rs1107748	39129340	C/T	0.321	0.304	0.515	0.92 (0.73-1.17)
		rs7220711	39145491	G/A	0.320	0.313	0.775	1.03 (0.82-1.29)
		rs1513670	39162857	C/T	0.420	0.398	0.407	0.91 (0.74-1.13)
17q21	*HDAC5*	rs228769	39548711	C/G	0.398	0.391	0.829	0.97 (0.70-1.34)
18q21	*TNFRSF11A*	rs884205	58205837	A/C	0.036	0.084	0.015	2.47 (1.16-5.25)
		rs3018362	58233073	G/A	0.209	0.199	0.715	1.06 (0.77-1.47)

MAF = minor allele frequency; OR = odds ratio; CI = confidence interval. [a] The former allele represents the minor allele.