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The Genetic Variations of *SQSTM1* Gene are Associated with Bone Density in the Korean Population

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Osteoporosis is a complex systemic skeletal disease and a major public health concern worldwide. It is a heritable disorder characterized mainly by low bone density and/or low trauma osteoporotic fractures, both of which have strong genetic determination. However, the specific genetic variants determining risk for low bone density are still largely unknown. Here, we performed association analysis to elucidate the possible relationship between genetic polymorphisms in the *SQSTM1* gene and low bone density. By examining a total of 7225 (men: 3622, women: 3603) subjects from the Korean population in the Korean Association REsource (KARE) study, we discovered that *SQSTM1* gene polymorphisms were associated with bone density. The results of the BD-RT (bone density estimated by T-score at distal radius) showed that three SNPs (rs513235, rs3734007, and rs11249661) within the *SQSTM1* gene were significantly associated with bone density. The results of the BD-TT (bone density estimated by T-score at midshaft tibia) showed that four SNPs (rs513235, rs3734007, rs2241349, and rs11249661) were significantly associated with bone density. The three SNPs (rs513235, rs3734007, and rs11249661) had common significance in both BD-RT and BD-TT. In summary, we found statistically significant SNPs in the *SQSTM1* gene that are associated with bone density traits. Therefore, our findings suggest *SQSTM1* gene could be related to pathogenesis of osteoporosis.

Key words : Bone density, *SQSTM1*, SNP, association

Introduction

Bone density is a medical term referring to the amount of matter per square centimeter of bones, and used in clinical medicine as an indirect indicator of osteoporosis and fracture risk. Bone density measurements are used to screen women for osteoporosis risk and to identify those who might benefit from measures to improve bone strength [3].

The sequestosome-1 protein is encoded by the *SQSTM1* gene, which is located in chromosome 5q35 region and sequestosome-1 binds ubiquitin and regulates activation of the nuclear factor kappa-B (NF-κB) signaling pathway [7,13]. Mutations in this gene result in sporadic and familial Paget disease of bone [6,8]. Paget disease of bone (PDB) is a common metabolic bone disease characterized by increased and disorganized bone turnover [11]. These abnormalities disrupt normal bone architecture and lead to various complications such as bone pain, bone deformity, deafness, nerve compression syndromes, pathological fracture and secondary osteoarthritis [12]. Genetic factors play an important role in PDB and mutations or polymorphisms have been identified in four genes that cause classical Paget's disease and related syndrome. These include *TNFRSF11A*, which encodes RANK, *TNFRSF11B* which encodes osteoprotegerin, *VCP* which encodes p97, and *SQSTM1* which encodes p62. All of these genes play a role in the RANK-NFκB signaling pathway and it is likely that the mutations predispose to PDB by disrupting normal signaling, leading to osteoclast activation [11], and underscoring the critical importance of this signaling pathway in bone metabolism and bone disease.

Despite of *SQSTM1* is genetic factor causing PDB, there is rarely a report about association with *SQSTM1* and bone density. In this study, we examined the association with genetic variations in *SQSTM1* and bone density in the Korean population. Notably, this study provides insight into the relation with *SQSTM1* and bone density.

Materials and Methods

Subjects and clinical characteristics

Subjects in the Korean population in the Korean Association REsource (KARE) study were described in more detail by other study [1]. Briefly 10,038 persons in the

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Ansung-Ansan prospective community cohorts were recruited. The initial numbers of subjects who were aged 40 to 69 years from Ansung and Ansan were 5018 and 5020, respectively. Of the 10,038 subjects, 1196 were excluded due to poor genotyping data. In addition, 1291 subjects who were on drug treatments that were also excluded.

It was investigated that 7225 subjects measured bone density among remaining subjects. Their basic characteristics-eg, bone density measures- are described in Table 1. Bone density is a proxy measurement for bone strength, which is the resistance to fracture, widely used to screen for osteoporosis. Bone density was estimated by T-score by dividing the difference of measured SOS (speed of sound) from mean SOS in healthy young adult population by the standard deviation of SOS in young adult population. Bone SOS was measured quantitative ultrasound at distal radius or mid-shaft tibia in the subjects of the KARE study. This study was approved by the institutional review board of the Korean National Institute of Health (KNIH). Written informed consent was obtained from all subjects.

Genotyping and selection of SNPs

The detailed genotyping and quality control processes were reported in Cho et al. [1]. Briefly, most DNA samples were isolated from the peripheral blood of participants and genotyped using the Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix, Inc., Santa Clara, CA, USA). The accuracy of the genotyping was calculated by Bayesian Robust Linear Modeling using the Mahalanobis Distance (BRLMM) algorithm [10]. Samples that had genotyping accuracies were lower than 98%, high missing genotype call rates (≥4%), high heterozygosity (>30%), or gender biases were excluded.

The SNPs that we analyzed were selected from the KARE data, based on their positions within the gene boundary (20 kb upstream and downstream of the first and last exons, respectively) (Table 2). The positions of the SNPs were validated in the NCBI database (http://www.ncbi.nlm.nih.gov). The clinical information and genotype data that we used were graciously provided by the Center for Genome Science, KNIH, Korea Center for Disease Control (KCDC).

Statistical analysis

Most statistical analyses were performed using PLINK version 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink) and PASW Statistics version 17.0 (SPSS Inc., Chicago, IL, USA). Linear regression was used to analyze BD-RT (bone density estimated by T-score at distal radius) and BD-TT (bone density estimated by T-score at midshaft tibia) as quantitative traits in the final 7225 subjects, controlling for cohort, age, and sex as covariates.

All association tests were based on an additive, dominant, or recessive model, and *p*-values were not adjusted for multiple tests. Statistical significance was determined at a two-tailed value of $p<0.05$.

Results

Association analysis with SNPs in *SQSTM1* gene and bone density

We informed the *SQSTM1* gene and its SNPs (Table 2). And, the basic characteristics of study subjects were shown to Table 1. The mean age of the 7225 study subjects was

Table 1. Basic characteristics of study subjects

	Total Mean±SD (no.)	Men Mean±SD (no.)	Women Mean±SD (no.)	*p* value*
Age (yr)	51.55±8.81 (7225)	51.29±8.70 (3622)	51.80±8.91 (3603)	0.014
Bone density				
Distal Radius T score	0.18±1.39 (7153)	0.17±1.20 (3606)	0.18±1.56 (3547)	0.809
Midshaft Tibia T score	-0.31±1.49 (7187)	0.25±1.16 (3617)	-0.89±1.56 (3570)	<0.0001

*Significant differences in phenotypes between men and women were compared using student's t-test

Table 2. Information of studied SNPs in *SQSTM1* gene

No.	SNP	Position, bp	Minor allele	MAF	Function
1	rs513235	179181705	T	0.241	Intron 1
2	rs3734007	179185143	T	0.160	Intron 5
3	rs2241349	179192615	C	0.328	Intron 5
4	rs2303676	179201681	A	0.246	Downstream
5	rs11249661	179210480	C	0.175	Downstream

51.55 years, that of men (n=3622) was 51.29 years, that of women (n=3603) was 51.80 years. The mean BD-RT of the 7153 subjects was 0.18±1.39, and the mean BD-TT of the 7187 subjects was -0.31±1.49 (Table 1). But, the mean and variance of BD-TT was statistically different between sex groups (men: 0.25±1.16, women: -0.89±1.56, p<0.0001) by Student's T-test in Table 1.

Linear regression analysis was used to associate genotypes with bone density traits, controlling for age, sex, and cohort as covariates. The results of associations on the five SNPs of *SQSTM1* gene in total, men, or women subjects were listed in Table 3.

The results on the BD-RT, three SNPs (rs513235, rs3734007, and rs11249661) were significantly associated with bone density in total or subjects divided by sex (Table 3). The SNP rs513235 had significance in men (β=0.080, additive p=0.013, recessive p=9.2×10^{-4}), and the SNP rs3734007 also had significance in men (β=0.054, recessive p=0.014). The SNP rs11249661 was significantly associated in total (β=0.038, recessive p=0.037) and men (β=0.066, recessive p=5.4×10^{-3})

The results on the BD-TT, four SNPs (rs513235, rs3734007, rs2241349, and rs11249661) were significantly associated with bone density in total or subjects divided by sex (Table 3). The SNP rs513235 had significance in total (β=0.069, additive p=7.2×10^{-3}, dominant p=0.026, recessive p=0.024), and women (β=0.085, additive p=0.025, dominant p=0.027). And the SNP rs3734007 had only significance in total (β=0.077, additive p=0.010, dominant p=4.3×10^{-3}). The SNP rs2241349 was significantly associated in total (β=0.062, additive p=8.3×10^{-3}, dominant p=0.029, recessive p=0.033) and men (β=0.062, additive p=0.030, dominant p=0.021). And the last SNP rs11249661 was significantly associated only in total (β=0.081, additive p=4.9×10^{-3}, dominant p=3.1×10^{-3}). The three SNPs (rs513235, rs3734007, and rs11249661) had commonly significance in both BD-RT and BD-TT.

Age-dependent associations with SNPs in *SQSTM1* gene and bone density

The most important risk factors for osteoporosis are advanced age (in both men and women), caused by a rapid reduction of bone density is related with estrogen deficiency following menopause in women, and a drop in testosterone levels had a similar effect in men. Therefore, we divided the subjects grouped into three subgroups by age (40s-, 50s-, and 60s-aged group). And, genetic variations of the present study were reanalyzed in the age (Table 4).

Genetic variations of *SQSTM1* in 40s-, and 60s-aged men were associated with BD-RT. But, three aged women were not at all associated with BD-RT. And all 50s-aged subjects had no association with both BD-RT and BD-TT. The highest significant SNP in BD-RT was rs513235 in 60s-aged men (β=0.196, additive p=8.7×10^{-3}, recessive p=2.3×10^{-4}) (Table 4).

And the results show that there were significance in 40s-aged men, and 60s-aged women with BD-TT. The highest significant SNP in BD-TT was also rs513235 the same in BD-RT, and there was association in 60s-aged women (β

Table 3. The associations with genetic variations of *SQSTM1* gene and bone density estimated by T-score, controlling for cohort, age, and sex

SNP	Minor allele	MAF	Total (n=7225)				Men (n=3622)				Women (n=3547)			
			beta±s.e.m.	Add p	Dom p	Rec p	beta±s.e.m.	Add p	Dom p	Rec p	beta±s.e.m.	Add p	Dom p	Rec p
BD-RT														
rs513235*	T	0.241	0.036±0.03	0.163	0.364	0.091	0.080±0.03	**0.013**	0.143	**9.2×10^{-4}**	-0.026±0.04	0.486	0.655	0.387
rs3734007*	T	0.160	0.036±0.03	0.222	0.334	0.223	0.054±0.04	0.142	0.430	**0.014**	-0.012±0.04	0.792	0.981	0.310
rs2241349	C	0.328	0.021±0.02	0.380	0.715	0.194	0.036±0.03	0.222	0.236	0.469	0.002±0.03	0.959	0.616	0.336
rs2303676	A	0.246	0.006±0.03	0.809	0.679	0.813	-0.013±0.03	0.683	0.770	0.097	0.023±0.04	0.536	0.677	0.478
rs11249661*	C	0.175	0.038±0.03	0.183	0.440	**0.037**	0.066±0.04	0.067	0.288	**5.4×10^{-3}**	-0.024±0.04	0.569	0.569	0.828
BD-TT														
rs513235*	T	0.241	0.069±0.03	**7.2×10^{-3}**	**0.026**	**0.024**	0.037±0.03	0.248	0.605	0.060	0.085±0.04	**0.025**	**0.027**	0.254
rs3734007*	T	0.160	0.077±0.03	**0.010**	**4.3×10^{-3}**	0.878	0.061±0.04	0.093	0.063	0.829	0.067±0.05	0.140	0.086	0.823
rs2241349	C	0.328	0.062±0.02	**8.3×10^{-3}**	**0.029**	**0.033**	0.062±0.03	**0.030**	**0.021**	0.321	0.057±0.04	0.102	0.323	0.053
rs2303676	A	0.246	-0.005±0.03	0.849	0.812	0.994	-0.010±0.03	0.751	0.896	0.588	-0.002±0.04	0.946	0.838	0.810
rs11249661*	C	0.175	0.081±0.03	**4.9×10^{-3}**	**3.1×10^{-3}**	0.459	0.059±0.04	0.092	0.069	0.717	0.073±0.04	0.091	0.071	0.763

Statistically significant (p<0.05) are indicated in bold and underline. *Significant SNPs in common BD-RT and BD-TT.
Abbreviations: MAF: Minor allele frequency; BD-RT, bone density estimated by T-score at distal radius; BD-TT, bone density estimated by T-score at midshaft tibia; s.e.m.: standard error.

Table 4. The age-dependent associations with genetic variations of *SQSTM1* gene and bone density estimated by T-score, controlling for cohort, age, and sex

Ages	Total				Men				Women			
SNP	beta±s.e.m.	Add *p*	Dom *p*	Rec *p*	beta±s.e.m.	Add *p*	Dom *p*	Rec *p*	beta±s.e.m.	Add *p*	Dom *p*	Rec *p*
BD-RT												
40s		**n=3651**				**n=1887**				**n=1764**		
rs513235	0.029±0.03	0.349	0.384	0.553	0.103±0.04	**0.010**	**0.040**	**0.020**	-0.054±0.05	0.255	0.467	0.163
rs3734007	0.049±0.04	0.178	0.187	0.555	0.080±0.05	0.087	0.147	0.153	0.012±0.06	0.832	0.658	0.489
rs2241349	0.019±0.03	0.497	0.691	0.415	0.028±0.04	0.443	0.349	0.879	0.012±0.04	0.793	0.756	0.272
rs2303676	-0.017±0.03	0.585	0.684	0.582	-0.048±0.04	0.246	0.899	**5.4×10^{-3}**	0.008±0.05	0.865	0.566	0.113
rs11249661	0.043±0.04	0.224	0.318	0.274	0.078±0.05	0.088	0.139	0.189	0.004±0.05	0.946	0.997	0.813
50s		**n=1800**				**n=910**				**n=890**		
rs513235	-0.040±0.06	0.478	0.329	0.760	-0.083±0.07	0.249	0.253	0.621	0.013±0.08	0.874	0.924	0.524
rs3734007	-0.014±0.06	0.829	0.757	0.851	-0.077±0.08	0.333	0.234	0.836	0.071±0.10	0.477	0.402	0.887
rs2241349	0.017±0.05	0.724	0.832	0.675	0.039±0.06	0.539	0.483	0.842	0.007±0.08	0.929	0.898	0.675
rs2303676	0.045±0.05	0.388	0.324	0.856	0.068±0.07	0.324	0.290	0.748	0.031±0.08	0.692	0.584	0.928
rs11249661	-0.019±0.06	0.762	0.498	0.339	-0.040±0.08	0.611	0.417	0.527	0.018±0.10	0.851	0.948	0.663
60s		**n=1698**				**n=805**				**n=893**		
rs513235	0.103±0.05	0.060	0.210	**0.026**	0.196±0.07	**8.7×10^{-3}**	0.150	**2.3×10^{-4}**	0.012±0.08	0.882	0.688	0.612
rs3734007	0.022±0.06	0.724	0.861	0.110	0.134±0.08	0.110	0.395	**8.9×10^{-3}**	-0.096±0.09	0.297	0.301	0.666
rs2241349	0.022±0.05	0.654	0.911	0.439	0.052±0.07	0.440	0.700	0.313	-0.007±0.07	0.924	0.848	0.907
rs2303676	-0.001±0.05	0.982	0.731	0.454	-0.030±0.07	0.688	0.682	0.850	0.025±0.08	0.742	0.418	0.400
rs11249661	0.028±0.06	0.641	0.932	0.100	0.145±0.08	0.075	0.358	**4.0×10^{-3}**	-0.096±0.09	0.283	0.331	0.475
BD-TT												
40s		**n=3644**				**n=1887**				**n=1757**		
rs513235	0.024±0.03	0.463	0.441	0.774	0.035±0.04	0.398	0.720	0.163	0.007±0.05	0.894	0.509	0.310
rs3734007	0.056±0.04	0.150	0.082	0.729	0.115±0.05	**0.019**	**0.011**	0.659	-0.016±0.06	0.793	0.972	0.276
rs2241349	0.055±0.03	0.070	**0.031**	0.690	0.106±0.04	**5.7×10^{-3}**	**1.7×10^{-3}**	0.357	0.004±0.05	0.934	0.889	0.957
rs2303676	-0.001±0.03	0.971	0.901	0.868	-0.050±0.04	0.244	0.495	0.113	0.031±0.05	0.530	0.951	0.146
rs11249661	0.054±0.04	0.152	0.108	0.928	0.105±0.05	**0.027**	**0.026**	0.396	-0.005±0.06	0.938	0.866	0.446
50s		**n=1801**				**n=913**				**n=888**		
rs513235	0.063±0.05	0.238	0.537	0.067	0.052±0.07	0.435	0.438	0.742	0.083±0.08	0.305	0.681	0.064
rs3734007	0.044±0.06	0.465	0.422	0.942	-0.037±0.07	0.614	0.757	0.454	0.144±0.10	0.140	0.123	0.739
rs2241349	0.042±0.05	0.359	0.675	0.191	-0.011±0.06	0.848	0.573	0.629	0.099±0.07	0.177	0.255	0.287
rs2303676	0.005±0.05	0.915	0.939	0.676	0.035±0.06	0.571	0.970	0.128	0.001±0.07	0.991	0.764	0.582
rs11249661	0.057±0.06	0.335	0.299	0.869	-0.009±0.07	0.894	0.958	0.569	0.141±0.09	0.130	0.107	0.772
60s		**n=1738**				**n=813**				**n=925**		
rs513235	0.151±0.05	**4.7×10^{-3}**	**0.019**	**0.019**	0.034±0.07	0.628	0.905	0.144	0.252±0.08	**1.2×10^{-3}**	**1.8×10^{-3}**	0.080
rs3734007	0.125±0.06	**0.041**	**0.038**	0.426	0.053±0.08	0.509	0.569	0.605	0.167±0.09	0.062	0.057	0.517
rs2241349	0.095±0.05	0.054	0.209	**0.036**	0.043±0.06	0.501	0.429	0.845	0.132±0.07	0.069	0.449	**6.5×10^{-3}**
rs2303676	-0.029±0.05	0.586	0.877	0.295	0.029±0.07	0.677	0.476	0.718	-0.075±0.08	0.326	0.466	0.322
rs11249661	0.118±0.06	**0.046**	0.055	0.292	0.040±0.08	0.609	0.577	0.905	0.173±0.09	**0.049**	0.074	0.195

Statistically significant (p<0.05) are indicated in bold and underline. Abbreviations: BD-RT, bone density estimated by T-score at distal radius; BD-TT, bone density estimated by T-score at midshaft tibia; s.e.m.: standard error.

=0.252, additive $p=1.2\times10^{-3}$, dominant $p=1.8\times10^{-3}$) (Table 4).

Discussion

In this study, we had investigated the genetic variation of *SQSTM1* with bone density using total 7225 subjects (men: 3622, women: 3603) in the KARE study (Table 1). As a result, we investigated 5 SNPs with bone density (Table 3, 4).

The association study showed that the 3 SNPs were significant for the BD-RT, and 4 SNPs were significant for the

BD-TT. The 3 SNPs (rs513235, rs3734007, and rs11249661) were found to be significant in both BD-RT and BD-TT (Table 3). Moreover, the all significant SNPs had negative beta values, and those means that the carrier of minor allele had strength bone density, and also resistance for osteoporosis. The SNPs of *SQSTM1* were also shown age-dependent characteristic association with bone densities (Table 4). And the 3 SNPs (rs513235, rs3734007, and rs11249661) had all negative beta values in significant age-divided subjects, therefore these 3 SNPs would be contribute strength of bone density, and slow the pathogenesis of osteoporosis.

Limitations of this study included the lack of detailed covered SNPs in the *SQSTM1* gene, but this report has the value of association study for *SQSTM1* and bone density. And, this study present that *SQSTM1* gene is clinically relevant to not only Paget's disease but also bone density. But in the near future, it is necessary to verify the relation of *SQSTM1* function for bone density or osteoporosis biologically.

In some PDB families exhibiting autosomal dominant inheritance, as well as some sporadic cases, domain-specific mutations in *SQSTM1/p62*, the gene encoding sequestosome-1, have been identified [6,8]. Laurin et al. found a Proline-Leucine mutation affecting codon 392 (P392L) in the ubiquitin-associated (UBA) domain of the *SQSTM1* protein an important cause of PDB in French Canadians [8]. The *SQSTM1* gene encodes p62 which is a scaffold protein that plays an important role in regulating NFκB signaling downstream of the IL-1 receptor, TNF receptor, RANK receptor and nerve growth factor receptor [9]. Mutation screening of families previously reported to have linkage to the PDB2 region [2] and the PDB7 region [5] has shown that most affected subjects carried mutations in the *SQSTM1* gene. Studies in mice with targeted inactivation of *SQSTM1* have shown impaired osteoclastogenesis in response to PTHrP injection *in vivo*, indicating that p62 play a role in regulating osteoclast function and activity in response to bone resorbing stimuli [4].

PDB shows a strong age-dependency; it is rarely diagnosed below the age of 50 but becomes progressively more common thereafter, to affect about 8% of men and 5% of women in the UK by the age of 80 [12].

It may be possible that mutations or polymorphisms of *SQSTM1* interfere with their ability to chaperone other signaling proteins to the proteasome, leading to activation of signaling and possibly contribute to the formation of nuclear inclusions which might be composed of protein aggregates that may cause osteoclast specific gene expression.

In summary, we investigated the presence of bone density-associated SNPs in *SQSTM1* gene. And, we found statistically significant SNPs that are associated with bone density traits. Therefore, this study suggests *SQSTM1* gene could be related to pathogenesis of osteoporosis.

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초록 : 한국인에서 골밀도와 *SQSTM1* 유전자 변이의 연관성

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골다공증은 복합적 전신 골격 질환으로, 공중 보건 분야의 전세계적인 주요한 관심 질환의 한 가지이다. 골다공증은 유전적 영향을 받는 질환으로, 낮은 골밀도와 적은 외력 의한 골다공성 골절 등의 특징을 보이며, 강한 유전성을 나타내는 질환이다. 그러나, 낮은 골밀도과 연관된 특정한 유전자의 다형성은 아직까지 많이 알려져 있지 않다. 본 연구에서는 *SQSTM1* 유전자의 유전적 다형성과 낮은 골밀도 사이의 상관성을 확인하기 위해, 한국인 유전체 연구(Korean Association Resource, KARE)에서 골밀도를 측정한 7,225명(남성: 3,622명, 여성: 3,603명)을 대상으로 *SQSTM1* 유전자 다형성과 골밀도 간의 선형 회기 분석을 하였다. BD-RT (원위 요골의 T 점수로 예측한 골밀도)에서 *SQSTM1* 유전자에서 3개의 SNP (rs513235, rs3734007, rs11249661)가 유의한 상관성이 있는 것으로 나타났으며, BD-TT (중위 경골의 T 점수로 예측한 골밀도)에서는 4개의 SNP (rs513235, rs3734007, rs2241349, rs11249661)가 유의한 상관성이 있는 것으로 나타났다. 특히 3개의 SNP (rs513235, rs3734007, rs11249661)는 BD-RT와 BD-TT 두 종류의 골밀도에서 공통적으로 유의한 상관성을 보였다. 이러한 결과로 미루어 골밀도와 *SQSTM1* 유전자의 다형성 간에 통계적으로 유의한 상관성을 가지며, *SQSTM1* 유전자는 골다공증의 발병과정에 관련이 있을 것으로 사료된다.