Research Article

The rs1634330 Polymorphisms in the SOST Gene Are Associated with Body Composition in Chinese Nuclear Families with Male Offspring

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Objective. The purpose of this study was to explore the effect of the SOST gene polymorphisms on body composition in Chinese nuclear families with male offspring. Methods. 1,016 individuals were recruited from 335 Chinese nuclear families with male offspring. We genotyped the 10 tagged single-nucleotide polymorphisms (SNPs) in SOST gene (rs7220711, rs865429, rs851057, rs1708635, rs2023794, rs1234612, rs74252774, rs1634330, rs851058, and rs1513670) in all the above people. We used dual-energy X-ray absorptiometry to measure the composition of the human body. The quantitative transmission disequilibrium test (QTDT) was used to analyze the association of the SNPs with the body composition. Results. QTDT analysis showed that rs1634330 was significantly associated with trunk LM ($P < 0.05$). However, haplotypes were not found to be significantly associated with the body composition in the within-family association. The 1000 permutations were consistent with these within-family association results. Conclusions. Our results showed that the genetic variation in the SOST gene may contribute to variations in the body composition of Chinese male offspring.

1. Introduction

The SOST gene is located on the long arm of human chromosome 17 (17q12–q21), encoding the sclerostin protein of 213 amino acids which negatively regulates bone formation through the Wnt pathway [1, 2]. Loss of function mutations of the SOST gene in human can lead to sclerosteosis or Van Buchem disease, an autosomal recessive disease with abnormal high bone mass [3, 4]. In contrast, SOST over-expressing mice had a low bone mass phenotype [5]. And pharmacological inhibitors (Romosozumab, etc.) of sclerostin can promote bone formation and inhibit bone resorption in postmenopausal women and men with osteoporosis [6, 7]. The body composition is composited of fat mass (FM) and lean mass (LM), which can be measured by dual-energy X-ray absorptiometry (DXA). In recent years, many studies focused on the association of body composition and Wnt pathway genes. The single-nucleotide polymorphisms (SNPs) of the LRP5 gene are not an important genetic marker contributing to body composition in Chinese and Caucasian young adults [8, 9]. Our previous study found evidence of an association between body composition and CTNNB1and WNT5B gene [10]. In the SOST gene, the rs10534024 is associated with body composition in Danish young men [11], but rs4792909, rs851054, and rs2023794 are not in Caucasian young men [8]. So, we conducted family-
based [quantitative transmission disequilibrium test (QTDT)] studies of 10 tag single-nucleotide polymorphisms (SNPs) in the SOST gene to ascertain the effect of SOST genetic variations on FM and LM in Chinese nuclear families with male offspring.

2. Materials and Methods

2.1. Subjects. The study was approved by the Independent Ethics Committee of the Shanghai Jiao Tong University Affiliated Sixth People’s Hospital. All the subjects involved in this study signed informed consent documents before entering the project. The recruited subjects were the local population of Shanghai City on the Middle East Coast of China by the Department of Osteoporosis and Bone Diseases. The inclusion and exclusion criteria in this study were detailed as before [12]. From 2004 to 2007, 349 nuclear families from Chinese Han nationality were recruited, including both parents, with a total of 1058 people. The nuclear family has at least one male offspring with an average age of 18–44 years. The age, gender, medical history, and family history of each subject were recorded.

2.2. Body Composition Measurements. All subjects underwent body composition measurements with a lunar prodigy DXA densitometer (GE Healthcare, Madison, WI, USA). Such a tool allows for the evaluation of fat mass (FM) (kg) and lean mass (LM) (kg) (including arms, legs, trunk, and total body) by conducting by the same well-trained technologist throughout the study. The method of machine calibration and the coefficient of variation (CV) of DXA in total body) by conducting by the same well-trained technologist throughout the study. The method of machine calibration and the coefficient of variation (CV) of DXA in measuring lean meat and fat were the same as before [12, 13]. Height and body weight were estimated using standardized equipment. BMI was estimated by dividing the weight in kilograms by the square of the height in meters. The percentage of fat mass (PFM) and the percentage of lean mass (PLM) were estimated as the ratio of fat mass and lean mass to body weight, respectively.

2.3. SNP Selection. The candidate SNPs in the SOST gene were evaluated as before [14]. The recruitment criteria were as follows: (1) validation status, especially in Chinese; (2) minor allele frequencies >0.05; (3) pairwise linkage disequilibrium (LD) exceeds a threshold \( r^2 \) of 0.8; and (4) classification as tag SNPs. Hence, 10 tag SNPs were selected which are located in 3′ flanking (rs7220711 and rs1513670), intron 2 (rs865429), and 5′ flanking (rs1234612, rs851058, rs1634330, rs1708635, rs74252774, rs2023794, and rs851057), respectively.

2.4. Genotyping. Genomic DNA was obtained from peripheral venous blood samples of every participant and genotyped the 10 tag SNPs. Using a SNaPshot SNP genotyping technique to genotype the SNPs. Primers were designed by online Primer3 software (http://bioinfo.ut.ee/primer3-0.4.0/). 10 pairs of PCR primers were designed to amplify 10 fragments of 136–241 bp in 10 loci, and 10 extended primers adjacent to the SNP loci were designed for single-base extension (the primer sequence is shown in Table 1). The PCR products were obtained by multiplex PCR using the HotStarTaq (Qiagen). After being purified by the shrimp alkaline enzyme (SAP, Promega) and the exosome I (Epicentre), the PCR products were extended by SNaPshot Multiplex kit (ABI). The extended products were purified by SAP and then sampled on ABI 3730 XL. SNP genotyping was analyzed with GeneMapper 4.1 (Applied Biosystems).

2.5. LD and Haplotype Analyses. In this study, the Haploview program (version 4.2) was used to generate Linkage disequilibrium (LD) plots of SNPs from SNP genotyping data [15]; \( D’ \) represented the degree of LD of the SNPs in the SOST gene. Haplotypes were constructed as mentioned above [14]. The frequencies of the genotypes and haplotypes were calculated using a group of unrelated parents of nuclear families.

2.6. Statistical Analyses. Allele frequencies were evaluated by simple counting. Hardy–Weinberg equilibrium (HWE) was calculated by a \( \chi^2 \) goodness-of-fit statistical test. The orthogonal model in the QTDT program was used to test for population stratification, linkage, and the within-family association between SNPs and haplotypes and body composition phenotypes. The QTDT software package is available online on the Internet (http://csg.sph.umich.edu/abecasis/QTDT/). In this model, founder and sibling genotypes are included in the within-family and the trio-based transmission disequilibrium test (TDT) is extended to quantitative trait data. The BMI was adjusted by age as a covariate. Gender was not used as a covariate because all the offspring were males. We only calculated the male offspring of the nuclear families and parents’ phenotypes were excluded in the QTDT. To avoid false-positive results generated in multiple tests in our study, permutations (1000 simulations) were performed to produce empirical \( P \) values [16–18]. All analyses considered that \( P < 0.05 \) was statistically significant.

After adjusting for age, the proportions of the variation in body composition of unrelated sons were obtained from the general linear model-ANOVA (GLM-ANOVA) explained by the SNPs. Statistical analysis was performed using the SPSS version 25.0 (SPSS Inc. of IBM, USA).

3. Results

3.1. Basic Characteristics of Study Subjects. Because of the poor quality of DNA, 7 subjects from 7 nuclear families were excluded, and 7 sons from 7 nuclear families deviated from Mendelian inheritance when initial QTDT analysis showed. So, the 14 families were removed from the study. Finally, we recruited 1,016 subjects from 335 male offspring nuclear families, including 670 parents and 346 sons. The basic characteristics of the subjects are reported in Table 2.

3.2. Tag SNPs Genotyping and Haplotype Frequency. 10 tag SNPs in the SOST gene were genotyped, and none were excluded from the further analysis. Each of the tag SNPs had
| Tag SNP's | Primers (forward/reverse) | Extended primers |
|-----------|---------------------------|------------------|
| rs7220711 | 5'-AGGAGCAGCTGCAAGGAAGACA-3' | 5'-TTTTTTTTTTTTAGTTCCCATTTAGTATAAAAGCTGGCTC-3' |
| rs1513670 | 5'-TGGCAACAGTGGCAGCTACAA-3' | 5'-GCCCCACATGCCAGGACAC-3' |
| rs865429  | 5'-GGAATGAGGCAAGGTTGGGACT-3' | 5'-TTTTTTTTTCCTGCAGTGTGCATTGCCCA-3' |
| rs851057  | 5'-GCCTTGGCCCTGCATATAATGA-3' | 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTCCCCCACGCCTCTACCTGC-3' |
| rs851058  | 5'-CCAGCAGAGCCGGTAGTGTTGT-3' | 5'-TTTTTTTTTTTTTTTTTTTAGGGTCATAGACAAGGGGAGGTGG-3' |
| rs74252774 | 5'-AAAGGAGGGGTGACTGCAGGAT-3' | 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGAAAGGAAAGGAAATCACGT-3' |
| rs1708635 | 5'-CGAGGCTGCAGTGAGCCATAC-3' | 5'-TTTTTTTTTTTTTTTTTTTTTTTTTGAGAYGGGGTCTCACTCTGTCA-3' |
| rs1634330 | 5'-GGAAGGAGGTGGGCAACAGG-3' | 5'-TGTGCACGCACACAGTAGAGGTTAA-3' |
| rs1234612 | 5'-CCCAGCCGATTTTTTTAAACATTGA-3' | 5'-TTTTTTTTATTAAACGTTTGGCGAGTGAACATC-3' |
| rs153670  | 5'-GCACACGGTTGTGGAAGCGGAC-3' | 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGAAAGGAAAGGAAATCACGT-3' |
a minor allele frequency (MAF) > 0.05 and was in Hardy–Weinberg equilibrium (HWE) (Table 3).

We calculated one block with the size of 31 kb of substantial LD in the SOST gene using Haploview (Figure 1). The common haplotypes for the block were represented by rs1634330, rs74252774, rs851057, rs2023794, rs851058, rs865429, rs1708635, and rs1513670. The 8 haplotypes accounted for 94.9% of the 670 unrelated parents (Table 4).

3.3. Association between Tag SNPs and Haplotypes with Body Composition Variations. The association between obesity-related phenotypes and single tag SNP in SOST was performed using QTDT for 335 male offspring nuclear families. There were 237, 243, 204, 238, 91, 228, 82, 230, 230, and 160 informative nuclear families for the TDT analysis at rs7220711, rs865429, rs851057, rs1708635, rs2023794, rs1234612, rs74252774, rs1634330, rs851058, and rs1513670, respectively. TDT results showed that population stratification were found for rs7220711 and arms FM (p = 0.0048), trunk FM (p = 0.0254), legs FM (p = 0.0092), and total LM (p = 0.0172); rs1513670 and arms and trunk FM (p = 0.0165 and 0.0070, respectively); and rs74252774 and total FM (p = 0.0303). The within-family associations were found for rs7220711 and total FM (p = 0.0080); rs1513670 and legs and total FM (p = 0.229 and 0.0070, respectively); rs851057 and arms, trunk and total FM (p = 0.0205, 0.0054 and 0.0141, respectively), and rs1634330 and trunk LM (p = 0.0049). In order to avoid the error caused by multiple parameters tests, we performed the permutation 1,000 tests. The association of rs1634330 and trunk LM (p = 0.0410) was found after the permutations (Table 5).

For haplotype-based association analyses, 231, 188, 186, 74, 43, and 44 informative nuclear families at TAGTGAT, TGTTGGAT, CACTAGTC, CACCATTC, CACTGGAT, and CAGTGGAT in the block were evaluated for the TDT analysis. However, we failed to find significant associations between any haplotypes and body composition in the permutation 1,000 tests (Table 6).

Besides, after adjusting for age as a covariate, we used ANOVA to obtain the proportion of changes in body composition explained by rs1634330. The rs1634330 explained 0.26% of the total variation in trunk LM.

4. Discussion

In our study, we measured the FM and LM of arms, trunk, legs, and total body and genotyped the 10 tag SNPs in the SOST gene of 335 male offspring nuclear families with 1,016 subjects from the Han ethnic group of China. We used QTDT to observe the association between polymorphisms in the SOST gene and body composition. We observed a significant within-family association between rs1634330 and the trunk FM. The 1000 permutations that were subsequently simulated were consistent with these within-family association results. We deem that the research of nuclear families is a better interpretation of the association between the polymorphisms in the SOST gene and body composition.

Given the above results of within-family association, the statistical power of our study sample to calculate a quantitative trait locus (QTL) in the TDT should be considered. First of all, the sample was composed of 335 nuclear families in China, including 670 parents and 346 sons. Family-based association analysis can avoid the impact of population stratification [19]. In addition, the heterozygosis of participants in our sample was high (MAF of 10 SNPs was > 0.06). On the whole, QTDT can use all the information in a pedigree to conduct powerful tests of association that are robust in the presence of stratification (http://csg.sph.umich.edu/abecasis/QTDT/). Finally, in order to evaluate the false positive and negative results caused by the multiple tests, 1,000 permutations were simulated. Although there was no statistical significance for the within-family association between single haplotype in SOST and body composition in this study, on account of our previous findings [10, 20], it can be said with certainty that our study sample is adequate to evaluate the potential QTL influencing on body composition variation; the results of this study should be more reliable because of the robustness of the TDT approach.

So far, two studies investigated the association between the polymorphism in the SOST gene and body composition [8, 11]. We observed the association between rs1634330 and
the trunk FM, in line with the findings of Piter et al. in Danish men from the Odense Androgen Study cohort. On the contrary, the study reported a lack of association between SOST polymorphisms and body composition in Caucasian adults from five different academic centers of Granada (Spain). The same to us is that they all choose young men as research objects and select SOST gene in body composition variations as study aim. But it is necessary to note that these studies are rather heterogeneous concerning the object ancestry (Chinese, Caucasian), gender (males and females), age (young and old), measurement methods of body composition (DXA, body composition analyzer, and light clothing), SNPs selection (tagged SNPs, reported previous association of body composition), and statistical method (QTDT, linear regression analysis, and multiple linear regression analysis).

Recent data [21] showed that SOST-/− mice have less body fat and smaller adipocytes, accompanied by improved glucose tolerance and enhanced insulin sensitivity. Contrarily, SOST overexpression mice demonstrated excess adipose tissue and impaired glucose handling. In SOST-/− mice white adipose tissue, Wnt signaling markers were upregulated.

Table 3: Information of the analyzed SOST tag SNPs.

| Tag SNP | Domain  | Polymorphism | Physical position | HWE | MAF in dbSNP (CEU) | MAF in dbSNP (CHB) | MAF in this study |
|---------|---------|--------------|-------------------|------|---------------------|---------------------|-------------------|
| rs7220711 | 3’ flanking | G/A | 41789965 | 0.827 | G:0.384 | G:0.272 | G:0.297 |
| rs1513670 | 3’ flanking | C/T | 41807331 | 0.278 | C:0.616 | C:0.388 | C:0.374 |
| rs865429 | Intron | G/A | 41835215 | 0.953 | G:0.121 | G:0.248 | G:0.278 |
| rs851057 | 5’ flanking | C/G | 41837264 | 0.935 | C:0.884 | C:0.364 | C:0.357 |
| rs2023794 | 5’ flanking | C/T | 41837660 | 0.242 | C:0.040 | C:0.087 | C:0.074 |
| rs851058 | 5’ flanking | A/G | 41837719 | 0.333 | A:0.364 | A:0.364 | A:0.306 |
| rs74252774 | 5’ flanking | G/T | 41838012 | 0.415 | G:1.000 | G:0.918 | G:0.934 |
| rs1708635 | 5’ flanking | T/A | 41838894 | 0.276 | T:0.606 | T:0.296 | T:0.317 |
| rs1634330 | 5’ flanking | C/T | 41839069 | 0.249 | C:0.606 | C:0.296 | C:0.317 |
| rs1234612 | 5’ flanking | C/T | 41840802 | 0.406 | C:0.303 | C:0.141 | C:0.169 |

SNP: single-nucleotide polymorphism; HWE: Hardy–Weinberg equilibrium; MAF: minor allele frequency; and dbSNP: SNP database.

Table 4: The structure and frequency of SOST haplotypes for all available SNPs.

| Index | rs1513670 | rs1634330 | rs1708635 | rs2023794 | rs7220711 | rs74252774 | rs851057 | rs851058 | Frequency |
|-------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 1     | T         | A         | G         | T         | G         | G         | A         | T         | 0.336     |
| 2     | T         | G         | G         | T         | G         | G         | A         | T         | 0.247     |
| 3     | C         | A         | C         | T         | A         | G         | T         | C         | 0.224     |
| 4     | C         | A         | C         | C         | A         | T         | T         | C         | 0.066     |
| 5     | C         | A         | C         | T         | G         | G         | A         | T         | 0.039     |
| 6     | C         | A         | G         | T         | G         | G         | A         | T         | 0.037     |

Figure 1: Linkage disequilibrium (LD) patterns for the SOST gene. The pairwise LD values (D’ × 100) of all SNPs are given in each diamond. D’ is calculated as D divided by the theoretical maximum for the observed allele frequencies. Bright red filled diamonds without values indicate a D’ = 1. One block with high LD was identified. Numbers in bracket indicate the length of the block.
increased and Bmp signaling indicators were reduced. In vitro and in vivo, Bmp4 and its receptor Bmpr1a levels were negatively correlated with the Wnt signaling levels in adipocytes. In vitro, Bmp antagonist noggin could abolish the effects of recombinant sclerostin on adipocyte metabolism. The above data showed that sclerostin indirectly regulated Bmp signaling to exhibit its effects on adipocyte metabolism. Osteocytes can stimulate myogenesis and strengthen muscle contractile function likely via the Wnt/β-catenin signaling. In the above progress, sclerostin inhibited muscle function by depressing both the effects of osteocyte-like cells and WNT3a on myoblasts differentiation [22]. The rs1634330 is located in the 5’ flanking which is next to the 5’ end of SOST. This region includes the promoter and may include enhancers or other protein binding sites. The primary function of this region is the regulation of gene transcription [23].
Further study is required to confirm whether rs1634330 might affect the binding of other proteins or regulation of gene transcription of SOST.

Of course, in our study, we also have several limitations. First, our nuclear families are small sample size that contained few sibling pairs and have only two generations, which lowered the power of the linkage analysis; second, the selection of SNPs was not based on functionality. We select a group of 10 tagged SNPs of the SOST gene that is mostly within a single large LD block, which results in less association between the SOST gene and body composition.

To our knowledge, this is the first time to study the relationship between the SOST gene polymorphism and the variation of body composition in the core family of male offspring. We found the genetic associations between the SOST gene and the body composition of Chinese male

| Table 6: P values of tests for population stratification, total association, and within-family association in SOST haplotypes using QTDT. |
|---------------------------------------------------------------|
| CACTGGAT | CACTAGTC | CACCATTC | CAGTGGAT | TGTTGGAT | TAGTGGAT |
| Tests of population stratification |
| BMI | 0.1345 | 0.7036 | 0.6155 | 0.5591 | 0.8234 | 0.9163 |
| Arms FM | 0.0785 | 0.3957 | 0.2127 | 0.0892 | 0.5264 | 0.933 |
| Trunk FM | 0.0568 | 0.3232 | 0.2205 | 0.0973 | 0.3628 | 0.0644 |
| Legs FM | 0.2020 | 0.8096 | 0.0718 | 0.0677 | 0.0967 | 0.4443 |
| Total FM | **0.0434** | 0.5896 | 0.1747 | 0.5626 | 0.0895 | 1.0000 |
| PFM | 0.4952 | 0.7563 | 0.3280 | 0.4137 | 0.9272 | 0.2319 |
| Arms LM | 0.0987 | 0.1793 | 0.4772 | 0.3501 | 0.3760 | 0.1518 |
| Trunk LM | **0.0303** | 0.0728 | 0.4102 | 0.6748 | 1.0000 | 0.1411 |
| Legs LM | 0.1733 | 0.4275 | 0.4275 | 0.2240 | 0.5944 | 0.2561 |
| Total LM | 0.0730 | 0.0845 | 0.1240 | 4e-005 | 1.0000 | 0.0531 |
| PLM | **0.0365** | 0.8282 | 0.4909 | 0.5839 | 0.7417 | 0.6347 |
| Tests of total association |
| BMI | 0.3953 | 0.6183 | 0.3097 | 0.9612 | 0.3564 | 0.0512 |
| Arms FM | **0.0105** | 0.3659 | 0.9312 | 0.9707 | 0.7207 | 0.0906 |
| Trunk FM | 0.0048 | 0.1507 | 0.8193 | 1.0000 | 0.8968 | 0.1262 |
| Legs FM | 0.0072 | 0.6696 | 0.9652 | 0.7794 | 0.9623 | 0.4744 |
| Total FM | **0.0164** | 1.0000 | 0.7718 | 0.7693 | 1.0000 | 0.1930 |
| PFM | 0.1041 | 0.7912 | 0.6941 | 0.7276 | 0.8148 | 0.9042 |
| Arms LM | 0.2736 | 0.3777 | 0.5566 | 0.7820 | 0.8393 | 0.7380 |
| Trunk LM | 1.0000 | 1.0000 | 1.0000 | 0.9348 | 1.0000 | 1.0000 |
| Legs LM | 0.2736 | 0.5674 | 0.6738 | 0.7456 | 1.0000 | 0.9580 |
| Total LM | **0.0299** | 0.2871 | 0.3573 | 1.0000 | 0.8362 | 0.8887 |
| PLM | 0.4696 | 0.9138 | 0.5649 | 0.8140 | 0.8730 | 0.6295 |
| Tests of within-family association |
| BMI | 0.0857 | 0.9137 | 0.3587 | 0.6015 | 0.5560 | 0.3028 |
| Arms FM | **0.0087** | 0.2485 | 0.2746 | 0.1440 | 0.6497 | 0.0243 |
| Trunk FM | 0.0041 | 0.1300 | 0.3120 | 0.2244 | 0.3492 | 0.0193 |
| Legs FM | 0.0254 | 0.6888 | 0.1074 | 0.1533 | 0.1195 | 0.3160 |
| Total FM | **0.0105** | 0.3215 | 0.2122 | 0.2295 | 0.6707 | 0.0204 |
| PFM | 0.7896 | 0.6866 | 0.5433 | 0.3850 | 0.9724 | 0.2876 |
| Arms LM | 0.3637 | 0.1087 | 0.7530 | 0.3517 | 0.3786 | 0.1621 |
| Trunk LM | 1.0000 | 0.0908 | 1.0000 | 0.9348 | 1.0000 | 1.0000 |
| Legs LM | 0.2736 | 0.5674 | 0.6738 | 0.7456 | 1.0000 | 0.9580 |
| Total LM | **0.1135** | 0.0430 | 0.3482 | 0.0748 | 0.6653 | 0.1095 |
| PLM | 0.1585 | 0.8092 | 0.7888 | 0.5596 | 0.8334 | 0.8953 |
| P 1000 permutation of within-family association |
| BMI | 0.1220 | 0.9080 | 0.4040 | 0.6430 | 0.5910 | 0.3360 |
| Arms FM | 0.1110 | 0.4720 | 0.5300 | 0.3360 | 0.7690 | 0.1490 |
| Trunk FM | 0.0820 | 0.3350 | 0.5010 | 0.3850 | 0.5280 | 0.1380 |
| Legs FM | 0.0561 | 0.7780 | 0.2460 | 0.2990 | 0.2760 | 0.5090 |
| Total FM | 0.1610 | 0.4870 | 0.4040 | 0.3860 | 0.7330 | 0.1410 |
| PFM | 0.7910 | 0.6150 | 0.4260 | 0.2010 | 0.9630 | 0.2220 |
| Arms LM | 0.4700 | 0.1030 | 0.7530 | 0.5680 | 0.4040 | 0.1880 |
| Trunk LM | 0.8480 | 0.7370 | 0.7420 | 0.1440 | 0.7540 | 0.0850 |
| Legs LM | 0.4440 | 0.2780 | 0.5140 | 0.1030 | 0.5810 | 0.9570 |
| Total LM | 0.4310 | 0.2490 | 0.5320 | 0.1830 | 0.7620 | 0.3440 |
| PLM | 0.1130 | 0.7580 | 0.7230 | 0.5070 | 0.7970 | 0.8850 |

BMI: body mass index; QTDT: quantitative transmission disequilibrium test; FM: fat mass; LM: lean mass; PFM: percentage of FM; and PLM: percentage of LM. BMI and body composition phenotype values are adjusted for age. Bold numbers indicate significant p values (p < 0.05).
offspring. The polymorphisms of rs1634330 in the SOST gene may contribute to variations in trunk LM of Chinese young men, but only 0.26% of the total variation in trunk LM (the coefficient of variation of the DXA measurements for LM is 1.12%) was explained by rs1634330. Additional research in larger sample populations and SNPs of the SOST gene with higher putative functionality is warranted to ascertain the role of the SOST gene in body composition variations.

Data Availability
The data used to support the findings of this study have not been made available because of the restrictions by the ethics in the hospital to protect patients’ privacy.

Conflicts of Interest
The authors declare that they have no conflicts of interest regarding the publication of this paper.

Authors’ Contributions
Luyue Qi and Liangyong Liu contributed equally to this study.

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References
[1] X. Li, Y. Zhang, H. Kang et al., “Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling,” Journal of Biological Chemistry, vol. 280, no. 20, pp. 19883–19887, 2005.
[2] R. L. V. Bezooijen, P. T. Dijke, S. E. Papapoulos, and C. W. G. M. Löwik, “SOST/sclerostin, an osteocyte-derived negative regulator of bone formation,” Cytokine & Growth Factor Reviews, vol. 16, no. 3, pp. 319–327, 2005.
[3] W. Van Hul, W. Balemans, E. Van Hul et al., “Van Buchem disease (hyperostosis corticalis generalisata) maps to chromosome 17q12-q21,” The American Journal of Human Genetics, vol. 62, no. 2, pp. 391–399, 1998.
[4] W. Balemans, J. Van Den Ende, A. Freire Paes-Alves et al., “Localization of the gene for sclerosteosis to the van Buchem disease-gene region on chromosome 17q12-q21,” The American Journal of Human Genetics, vol. 64, no. 6, pp. 1661–1669, 1999.
[5] I. Kramer, G. G. Loots, A. Studer, H. Keller, and M. Kneissel, “Parathyroid hormone (PTH)-induced bone gain is blunted in SOST overexpressing and deficient mice,” Journal of Bone and Mineral Research, vol. 25, no. 2, pp. 178–189, 2010.
[6] M. R. McClung, J. P. Brown, A. Diez-Perez et al., “Effects of 24 Months of treatment with romosozumab followed by 12 Months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study,” Journal of Bone and Mineral Research, vol. 33, no. 8, pp. 1397–1406, 2018.
[7] E. M. Lewiecki, T. Blicharski, S. Goemaere et al., “A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis,” The Journal of Clinical Endocrinology & Metabolism, vol. 103, no. 9, pp. 3183–3193, 2018.
[8] M. Correa-Rodriguez, J. Schmidt-RioValle, and B. Rueda-Medina, “The rs3736228 polymorphism in the LRP5 gene is associated with calcaneal ultrasound parameter but not with body composition in a cohort of young Caucasian adults,” Journal of Bone and Mineral Metabolism, vol. 35, no. 6, pp. 694–700, 2017.
[9] J.-B. Yu, Y.-H. Ke, J.-W. He et al., “No association between LRP5 gene polymorphisms and bone and obesity phenotypes in Chinese male-offspring nuclear families,” Acta Pharmacologica Sinica, vol. 31, no. 11, pp. 1464–1469, 2010.
[10] Y. Zheng, C. Wang, H. Zhang et al., “Polymorphisms in Wnt signaling pathway genes are associated with peak bone mineral density, lean mass, and fat mass in Chinese male nuclear families,” Osteoporosis International, vol. 27, no. 5, pp. 1805–1815, 2016.
[11] E. Pifers, F. De Freitas, T. L. Nielsen, M. Andersen, K. Brixen, and W. Van Hul, “Association study of polymorphisms in the SOST gene region and parameters of bone strength and body composition in both young and elderly men: data from the Odense Androgen Study,” Calcified Tissue International, vol. 90, no. 1, pp. 30–39, 2012.
[12] W.-J. Xiao, Y.-H. Ke, J.-W. He et al., “ALOX12 polymorphisms are associated with fat mass but not peak bone mineral density in Chinese nuclear families,” International Journal of Obesity, vol. 35, no. 3, pp. 378–386, 2011.
[13] H. Yue, J.-W. He, H. Zhang et al., “Contribution of myostatin gene polymorphisms to normal variation in lean mass, fat mass and peak BMD in Chinese male offspring,” Acta Pharmacologica Sinica, vol. 33, no. 5, pp. 660–667, 2012.
[14] L. Qi, S. Xiang, L. Li et al., “Association of SOST gene polymorphisms with peak bone mineral density in Chinese nuclear families with male-offspring,” Acta Biochimica et Biophysica Sinica, vol. 51, no. 3, pp. 341–343, 2019.
[15] J. C. Barrett, B. Fry, J. Maller, and M. J. Daly, “Haplview: analysis and visualization of LD and haplotype maps,” Bioinformatics, vol. 21, no. 2, pp. 263–265, 2005.
[16] G. R. Abecasis, L. R. Cardon, and W. O. C. Cookson, “A general test of association for quantitative traits in nuclear families,” The American Journal of Human Genetics, vol. 66, no. 1, pp. 279–292, 2000.
[17] L. M. McIntyre, E. R. Martin, K. L. Simonsen, and N. L. Kaplan, “Circumventing multiple testing: a multilocus Monte Carlo approach to testing for association,” Genetic Epidemiology, vol. 19, no. 1, pp. 18–29, 2000.
[18] Z.-L. Zhang, J.-W. He, Y.-J. Qin et al., “Association between myostatin gene polymorphisms and peak BMD variation in Chinese nuclear families,” Osteoporosis International, vol. 19, no. 1, pp. 39–47, 2008.
[19] R. L. Hanson, S. Kobes, R. S. Lindsay, and W. C. Knowler, “Assessment of parent-of-origin effects in linkage analysis of quantitative traits,” The American Journal of Human Genetics, vol. 68, no. 4, pp. 951–962, 2001.
[20] W.-J. Xiao, Y.-H. Ke, J.-W. He et al., “Polymorphisms in the human ALOX12 and ALOX15 genes are associated with peak bone mineral density in Chinese nuclear families,” Osteoporosis International, vol. 23, no. 7, pp. 1889–1897, 2012.
[21] S. P. Kim, J. L. Frey, Z. Li et al., "Sclerostin influences body composition by regulating catabolic and anabolic metabolism in adipocytes," *Proceedings of the National Academy of Sciences*, vol. 114, no. 52, pp. E11238–e11247, 2017.

[22] J. Huang, S. Romero-Suarez, N. Lara et al., "Crosstalk between MLO-Y4 osteocytes and C2C12 muscle cells is mediated by the wnt/β-catenin pathway," *JBMR Plus*, vol. 1, no. 2, pp. 86–100, 2017.

[23] S. Bortoli, M. Collinet, and B. Desbuquois, "Vanadate inhibits transcription of the rat insulin receptor gene via a proximal sequence of the 5‘flanking region," *Biochimie Open*, vol. 7, pp. 26–32, 2018.