Received: 26 April 2021 | Revised: 16 June 2021 | Accepted: 1 July 2021

DOI: 10.1002/mgg3.1747

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

The association between sarcopenia susceptibility and polymorphisms of *FTO*, *ACVR2B*, and *IRS1* in Tibetans

Xianpeng Zhang[1] | **Liping Ye**[2] | **Xin Li**[1] | **Ying Chen**[1] | **Yaqiong Jiang**[3] | **Wenhui Li**[1] | **Youfeng Wen**[1]

[1]Institute of Biological Anthropology, Jinzhou Medical University, Jinzhou, China

[2]Department of Pathophysiology, Jinzhou Medical University, Jinzhou, China

[3]Tama Community Health Center of Chengguan District, Lhasa, China

Correspondence
Youfeng Wen, Institute of Biological Anthropology, Jinzhou Medical University, Jinzhou, China.
Email: wenyf@jzmu.edu.cn

Funding information
This study was supported by grants from the National Natural Science Foundation of China (No. 31571233) and the scientific research project from the Education Department of Liaoning Province (No. JYTJCZR2020074).

Abstract

Background: Hypoxia within the plateau has a negative effect on skeletal muscle and may play a role in the development of sarcopenia in humans. Tibetans having lived in the Qinghai-Tibet Plateau for thousands of years, are a high-risk group for sarcopenia; however, they have a distinctive suite of genetic traits that enable them to tolerate environmental hypoxia and are genetically significantly different from Han Chinese and other lowland populations. Sarcopenia has been consistently found to be associated with single-nucleotide polymorphisms, but few studies have investigated the role of single-nucleotide polymorphisms in a range of muscle phenotypes and sarcopenia in Tibetan peoples.

Methods: Our study aimed to investigate the skeletal muscle mass and fat mass of 160 Tibetans (80 men and 80 women) from Lhasa (altitude of 3600 meters) and analyze the association between the polymorphisms of fat mass and obesity protein (*FTO*) rs9939609, *FTO* rs9936385, activin type IIB receptor (*ACVR2B*) rs2276541, insulin receptor substrate 1 (*IRS1*) 2943656 and sarcopenia.

Result: *FTO* rs9939609 and rs9936385 polymorphisms were associated with lower limb skeletal muscle mass and sarcopenia for Tibetan women, and TT homozygotes had a higher risk for sarcopenia. But *ACVR2B* rs2276541 and *IRS1* 2943656 polymorphisms were unassociated with sarcopenia in Tibetan.

Conclusion: In Tibetans, *FTO* rs9939609 and rs9936385 polymorphisms were associated with sarcopenia, and *ACVR2B* rs2276541 and *IRS1* 2943656 polymorphisms were unassociated with sarcopenia.

KEYWORDS

activin type IIB receptor (*ACVR2B*), fat mass and obesity-associated protein (*FTO*), insulin receptor substrate 1 (*IRS1*), sarcopenia, single-nucleotide polymorphism (SNP), Tibetan

1 | INTRODUCTION

Hypoxia has a negative effect on skeletal muscle, as it can cause hypoxia-induced muscle loss (Pasiakos et al., 2017). Changes in body composition, such as loss of skeletal muscle mass, frequently occur when humans are exposed to hypoxic environments (Dunnwald et al., 2019; Fusch et al., 1996; Wandrag et al., 2017). Hypoxia can increase the levels of circulating proinflammatory cytokines, leading to inflammation (Eltzschig & Carmeliet, 2011); it also causes an increase in reactive oxygen species, leading to oxidative damage (McGarry et al., 2018). Therefore, it may play a role in the development of sarcopenia in humans. In previous research, the incidences of sarcopenia in Tibetans over 60 were 17.2% in men and 36.0% in women, significantly higher than those in the plain population (Ye et al., 2020). Tibetans are an archaic ethnicity (Lu et al., 2016), have lived at very high altitudes for thousands of years, and have a distinctive suite of genetic traits that enable them to tolerate environmental hypoxia (Simonson et al., 2010; Song et al., 2020), which make them significantly different from the Han and other plain populations genetically (Beall et al., 2010). Recently, the association between single-nucleotide polymorphisms (SNPs) and sarcopenia was found, and some risk genotypes have been determined (Khanal et al., 2020; Roth et al., 2004), but few studies have investigated the role of SNPs in muscle phenotypes and sarcopenia in Tibetans. Therefore, we investigated whether the identified risk-genotypes for sarcopenia were equally applicable to Tibetans.

The fat mass and obesity-associated protein (*FTO*) gene has been shown to be related to obesity (Loos & Yeo, 2014). Its polymorphisms have been associated with obesity, fat mass, and obesity-related indicators, such as body mass index (BMI) in adults and children (Hinney et al., 2007; Livshits et al., 2012), which have been studied in various groups of people such as Europeans (Merra et al., 2020; Sällman Almén et al., 2013), Americans (Grant et al., 2008; Wing et al., 2009), and Mexicans (Villalobos-Comparán et al., 2008). The *FTO* gene has been associated not only with fat mass but also with lean mass (Ran et al., 2020; Sonestedt et al., 2011). C-allele carriers at rs9936385 have greater lean mass and the T allele is associated with sarcopenia (Karasik et al., 2019; Zillikens et al., 2017). A-allele carriers at rs9939609 have lower lean mass and AA homozygotes are more than 3-fold higher risk for sarcopenia compared to T-allele carriers (Khanal et al., 2020). *ACVR2B* codes for a receptor for a negative regulator of skeletal muscle, myostatin, and deletion in *ACVR2B* causes skeletal muscle hyperplasia (an increase in the number of skeletal muscle fibers) and hypertrophy (an increase in the size of skeletal muscle fibers) (Lee & McPherron, 2001; White & LeBrasseur, 2014). It has previously been identified as a gene of skeletal muscle mass and strength (Klimentidis et al., 2016; Walsh et al., 2007), A-allele carriers at rs2276541 have greater lean mass. Insulin receptor substrate 1 (*IRS1*) is a signaling adapter protein, it is downstream of the Insulin-like growth factor 1 (*IGF1*) receptor, *IGF1* induces skeletal muscle hypertrophy by activating the *IGF1*/*IRS1*/*PI3K*/*Akt* pathway (Z. Li et al., 2019), and loss of *IRS1* can limit the *IGF1* pathway and negatively affect skeletal muscle mass (Shi et al., 2011). *IRS1* is essential for skeletal muscle growth and protein homeostasis, and polymorphism of rs2943656 is associated with total body lean mass and appendicular lean mass (Zillikens et al., 2017). There is no research which has investigated the association between polymorphisms of *FTO* rs9939609, *FTO* rs9936385, *ACVR2B* rs2276541, *IRS1* 2943656 and sarcopenia in Tibetans.

2 | MATERIALS AND METHODS

2.1 | Study population

The survey was carried out via health examinations in August 2016 in Lhasa (altitude of 3600 m), China (Figure 1). Native Tibetans over 40 years of age participated in this study. A total of 1447 subjects (604 men and 843 women) were investigated, including 438 sarcopenia participants (200 men and 238 women) and 1009 healthy participants (404 men and 605 women). We randomly selected 160 adults (80 men and 80 women) from the sarcopenia group and healthy control group with an average age of 53.19 years. The following subjects were excluded from the study: (1) individuals under long-term bed rest, with sedentary lifestyles, or those who experienced extreme weight loss; (2) individuals with heart, lung, liver, kidney, or brain diseases, inflammatory reaction diseases, malignant tumors, or endocrine diseases; (3) individuals with an absorption disorder, gastrointestinal disease, anorexia, or drug use. The interviewers were trained before the survey. The study was approved by the Research Ethics Committee of Jinzhou Medical University in accordance with the Declaration of Helsinki. Verbal and written informed consent were obtained from all participants.

2.2 | Measurement

2.2.1 | Height

Height was measured using a portable stadiometer (HM200P, American Charder Company, America) and recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated from weight and height.

2.2.2 | Handgrip strength (HS)

HS was measured using a handheld dynamometer based on strain gauge sensors (CAMRY EH101) to the nearest

FIGURE 1 The map of sample collection place

0.1 kg. Both hands were tested with the participant seated, the elbow flexed at a 110° angle, wrist placed in a neutral position, and the interphalangeal joint of the index finger positioned at a 90° angle. Two readings were obtained for each hand, and the highest value for either hand was used for the analyses.

2.2.3 | Gait speed (GS)

According to the criteria of the Asian Working Group for Sarcopenia (AWGS) (Chen et al., 2014), the physical performance was assessed using the usual GS metric. To measure the GS, the participants were asked to walk a 6 m distance at their usual speed. Timing commenced when the participants started foot movement and stopped when the foot contacted the ground after completely crossing the 6 m mark. Canes or walkers were allowed if necessary.

2.2.4 | Weight, fat mass, and muscle mass

A bioelectrical impedance analyzer (MC-180, Bailida) was used to measure weight, fat mass (FM), skeletal muscle mass (SMM), trunk skeletal muscle mass (TSM), left upper limb skeletal muscle mass (LUSM), right upper limb skeletal muscle mass (RUSM), left lower limb skeletal muscle mass (LLSM), right lower limb skeletal muscle mass (RLSM), trunk fat mass (TFM), left upper limb fat mass (LUFM), right upper limb fat mass (RUFM), left lower limb fat mass (LLFM), and right lower limb fat mass (RLFM).

2.3 | Sarcopenia diagnosis

According to the recommended diagnostic AWGS algorithm, GS, HS, and skeletal muscle mass index (SMI) were the primary indicators for sarcopenia diagnosis (Chen et al., 2014).

The cutoff values for SMI measurements were 8.07 kg/m^2 for men and 6.62 kg/m^2 for women (Ye et al., 2020). Low physical performance was defined as a GS less than 0.8 m/s (Ye et al., 2020). The cutoff values for HS were <26.7 kg for men and <15.8 kg for women (Ye et al., 2020).

2.4 | DNA extraction

First, 2 ml of venous blood was collected from all participants and DNA was extracted from the whole peripheral blood sample using a DNA extraction kit (Blood DNA Extraction Kit, ELibio™). DNA samples were stored at −80°C before genotyping. After DNA extraction, the concentration of the extracted material was obtained using a spectrophotometer (BioPhotometer plus).

2.5 | PCR and genotyping

The primer information of DNA fragments containing the *FTO* rs9939609, *FTO* rs9936385, *ACVR2B* rs2276541 and *IRS1* rs2943656 was uploaded as supplementary material 1. For all polymorphism samples, the reactions were carried out in a 30 μl volume of 1 μl of DNA, 15 μl of 2XPCR MIX (TAKARA), 12 μl of DDW, and 1 μl of each primer. The PCR conditions were as follows: initial denaturation at 95°C for 3 min, followed by 35 cycles of denaturation at 94°C for 20 s, annealing at 58°C for 20 s and extension at 72°C for 40 s, and then a final extension at 72°C for 5 min. Genotypes for the *FTO* rs9939609 (TT/AT/AA), *FTO* rs9936385 (TT/CT/CC), *ACVR2B* rs2276541(AA/AG/GG), and *IRS1* rs2943656 (AA/AG/GG) polymorphism were determined using a 3730 XL Gene Sequencer (ABI).

2.6 | Statistical analyses

The Hardy–Weinberg equilibrium (HWE) was calculated to determine the variation in the distribution of alleles and genotypes within the population. The data are expressed as the mean ± standard deviation. The association between genotypes and anthropometric indices and body composition was analyzed via analysis of variance. The chi-square test was used to analyze the differences in genotype and allele frequency between the sarcopenia group and the control group. Logistic regression analyses were used to analyze the odds ratio (OR) and 95% confidence interval (95% Cl) of sarcopenia among the genotypes. All analyses were performed using SPSS (ver.25.0, IBM Company). The map of China was plotted by QGIS (https://www.qgis.org/).

3 | RESULTS

The basic characteristics of the samples are listed in Table 1. There were no significant differences in age and height between the sarcopenia and control groups in men and women ($p > 0.05$). Comparisons of the *FTO*s rs9939609, *FTO* rs9936385, *ACVR2B* rs2276541, and *IRS1* rs2943656 polymorphism between the sarcopenia and healthy groups are given in Tables 2–5, respectively. The genotypes in the healthy control and sarcopenia cohorts were in HWE. The genotype and allele frequencies of *FTO* were significantly different between the groups ($p < 0.05$), particularly for women. The frequency of the T allele was higher in the sarcopenia group than in controls for both SNPs. *FTO* rs9939609TT homozygotes exhibited a 2.414-fold higher risk for sarcopenia compared to A-allele carriers (OR = 2.414, CI: 1.270–4.586, $p = 0.007$), and *FTO* rs9936385 TT homozygotes exhibited a 2.414-fold higher risk for sarcopenia compared to C-allele carriers (OR = 2.414, CI: 1.270–4.586, $p = 0.007$). There was no difference of genotype and allele frequencies between health group and sarcopenia group in *ACVR2B* rs2276541 and *IRS1* rs2943656.

The associations among genotypes of *FTO*, *ACVR2B* and *IRS1*, body composition and anthropometric indices are listed in Tables 6–9, respectively. Both rs9939609 and rs9936385 were associated with lower limb skeletal muscle mass in Tibetan women, and genotypes AA/CC and AT/CT had higher lower limb skeletal muscle mass compared to TT, but there was no association between *FTO* genotypes and fat mass. And *ACVR2B* rs2276541 and *IRS1* rs2943656 were unassociated with body composition in Tibetans.

4 | DISCUSSION

Skeletal muscle strength and mass are strongly determined by genetics (Tan et al., 2012), and inter-individual variation in muscle phenotype may be attributed to genetic factors, environmental factors, and/or gene–environment interactions (Pratt et al., 2019). Previous studies have reported that skeletal muscle development is impaired and lean mass is significantly reduced in *FTO*-deficient mice (McMurray et al., 2013; Wang et al., 2017). Changes in *FTO* gene expression are associated with changes in skeletal muscle percentage (Doaei et al., 2019), but it has remained unclear how *FTO* affects skeletal muscle mass. *FTO* gene polymorphism in China has only been found in the Han (Huang et al., 2011) and Mongolian (Zhang et al., 2018) Chinese, but no research has involved the Tibetans. We found that the *FTO* rs9939609 and rs9936385 polymorphisms of Tibetan women were associated with lower limb skeletal muscle mass and sarcopenia. TT homozygotes were at higher risk for sarcopenia

TABLE 1 Anthropometric indices and body composition characteristics of the Tibetan people

	Male (80)			Female (80)		
Index	Control (40)	Sarcopenia (40)	*p*	Control (40)	Sarcopenia (40)	*p*
Age	53.73 ± 7.48	51.38 ± 7.20	0.156	52.45 ± 8.53	55.20 ± 8.08	0.143
Height	167.59 ± 6.38	169.40 ± 7.76	0.257	159.00 ± 5.08	157.38 ± 5.66	0.180
Weight	70.28 ± 9.42	57.44 ± 6.54	0.000	66.40 ± 9.15	53.19 ± 8.04	0.000
BMI	24.97 ± 2.67	19.98 ± 1.41	0.000	26.24 ± 3.39	21.42 ± 2.73	0.000
FFM	53.64 ± 5.38	47.48 ± 5.08	0.000	42.07 ± 3.25	37.51 ± 3.20	0.000
FM	16.68 ± 5.27	9.99 ± 3.28	0.000	24.34 ± 7.18	15.70 ± 5.73	0.000
SMM	50.85±5.12	45.00 ± 4.82	0.000	39.56 ± 2.97	35.38 ± 2.94	0.000
TSM	28.11 ± 2.56	25.57 ± 2.59	0.000	22.55 ± 1.53	21.13 ± 1.87	0.000
LUSM	2.75 ± 0.37	2.38 ± 0.31	0.000	2.05 ± 0.24	1.67 ± 0.15	0.000
LLSM	8.56 ± 1.05	7.27 ± 0.95	0.000	6.38 ± 0.69	5.42 ± 0.50	0.000
RUSM	2.85 ± 0.38	2.48 ± 0.30	0.000	2.15 ± 0.24	1.74 ± 0.17	0.000
RLSM	8.70 ± 1.13	7.41 ± 0.95	0.000	6.54 ± 0.66	5.54 ± 0.46	0.000
TFM	9.77 ± 3.30	5.74 ± 2.26	0.000	13.91 ± 4.58	8.75 ± 4.04	0.000
LUFM	0.64 ± 0.23	0.34 ± 0.13	0.000	1.17 ± 0.48	0.61 ± 0.28	0.000
LLFM	2.89 ± 0.81	1.86 ± 0.44	0.000	4.08 ± 0.88	2.90 ± 0.58	0.000
RUFM	0.60 ± 0.21	0.33 ± 0.12	0.000	1.15 ± 0.48	0.59 ± 0.28	0.000
RLFM	2.89 ± 0.82	1.83 ± 0.43	0.000	4.18 ± 0.89	2.98 ± 0.59	0.000
HS	31.95 ± 8.73	30.64 ± 6.88	0.460	21.41 ± 7.14	17.52 ± 4.77	0.005

Abbreviations: BMI, body mass index; FFM, fat-free mass; FM, fat mass; HS, handgrip strength; LLFM, left lower limb fat mass; LLSM, left lower limb skeletal muscle mass; LUFM, left upper limb fat mass; LUSM, left upper limb Skeletal muscle mass; RLFM, right lower limb fat mass; RLSM, right lower limb skeletal muscle mass; RUFM, right upper limb fat mass; RUSM, right upper limb skeletal muscle mass; SMM, skeletal muscle mass; TFM, trunk fat mass; TSM, trunk skeletal muscle mass.

TABLE 2 Comparison of *FTO* rs9939609 polymorphism between healthy controls and the sarcopenia group

	Genotype (%)					Allele (%)			
Group	TT	AT	AA	χ^2	p_1	A	T	χ^2	p_2
Sarcopenia	54 (67.5)	23 (28.75)	3 (3.75)	7.343	0.024	29 (18.125)	131 (81.875)	6.174	0.013
S-Male	28 (70.0)	10 (25.0)	2 (5.0)	2.198	0.370	14 (17.5)	66 (82.5)	1.345	0.246
S-Female	26 (65.0)	13 (32.5)	1 (2.5)	6.143	0.046	15 (18.75)	65 (81.25)	5.375	0.020
Control	37 (46.25)	38 (47.5)	5 (6.25)	—	—	48 (30.0)	112 (70.0)	—	—
C-Male	22 (55.0)	16 (40.0)	2 (5.0)	—	—	20 (25.0)	60 (75.0)	—	—
C-Female	15 (37.5)	22 (55.0)	3 (7.5)	—	—	28 (35.0)	52 (65.0)	—	—

(OR = 2.414, CI: 1.270–4.586, $p = 0.007$) (Figures 2 and 3). This risk genotype is in line with the results of Sonestedt et al., (2011), Karasik et al., (2019), Zillikens et al., (2017), and Khanal et al., (2020), but different from those of Khanal et al., (2020) and Heffernan et al. (2017). These apparent differences in genotypic associations could reflect genetic and environmental differences. The minor allele (A) frequency of rs9939609 was 24.06% for the total Tibetan population, 18.1% in the sarcopenia group, and 30.0% in the healthy control group. It was significantly diverse among different populations, being the highest in Turks (40.2%) and lowest in Mongolians (12.0%) (Table 10). Few studies have considered the *FTO* rs9936385 polymorphism, and the differences in allele frequency among populations are still unknown. In this study, the C allele frequency was 18.1% in the Tibetan sarcopenia group and 30.0% for healthy controls.

FTO is an upstream regulator of the mammalian target of rapamycin (mTOR) pathway, *FTO* linked amino acid availability and mammalian target of rapamycin complex 1 (mTORC1) signaling, which regulates growth and translation; cells lacking *FTO* display decreased activation of the mTORC1 pathway and increased autophagy (Gulati et al.,

TABLE 3 Comparison of *FTO* rs9936385 polymorphism between healthy controls and the sarcopenia group

	Genotype (%)					Allele (%)			
Group	**TT**	**CT**	**CC**	χ^2	p_1	**C**	**T**	χ^2	p_2
Sarcopenia	54 (67.5)	23 (28.75)	3 (3.75)	7.343	0.024	29 (18.125)	131 (81.875)	6.174	0.013
S-Male	28 (70.0)	10 (25.0)	2 (5.0)	2.198	0.370	14 (17.5)	66 (82.5)	1.345	0.246
S-Female	26 (65.0)	13 (32.5)	1 (2.5)	6.143	0.046	15 (18.75)	65 (81.25)	5.375	0.020
Control	37 (46.25)	38 (47.5)	5 (6.25)	—	—	48 (30.0)	112 (70.0)	—	—
C-Male	22 (55.0)	16 (40.0)	2 (5.0)	—	—	20 (25.0)	60 (75.0)	—	—
C-Female	15 (37.5)	22 (55.0)	3 (7.5)	—	—	28 (35.0)	52 (65.0)	—	—

TABLE 4 Comparison of *ACVR2B* rs2276541 polymorphism between healthy controls and the sarcopenia group

	Genotype (%)					Allele (%)			
Group	**AA**	**AG**	**GG**	χ^2	p_1	**A**	**G**	χ^2	p_2
Sarcopenia	24 (30.0)	36 (45.0)	20 (25.0)	0.436	0.804	84 (52.5)	76 (47.5)	0.050	0.823
S-Male	12 (30.0)	17 (42.5)	11 (27.5)	1.310	0.519	41 (51.25)	39 (48.75)	0.100	0.752
S-Female	12 (30.0)	19 (47.5)	9 (22.5)	0.857	0.651	45 (56.25)	35 (43.75)	1.601	0.206
Control	21 (26.25)	40 (50.0)	19 (23.75)	—	—	82 (51.25)	78 (48.75)	—	—
C-Male	12 (30.0)	21 (52.5)	7 (17.5)	—	—	43 (53.75)	37 (46.25)	—	—
C-Female	9 (22.5)	19 (47.5)	12 (30.0)	—	—	37 (46.25)	43 (53.75)	—	—

TABLE 5 Comparison of *IRS1* rs2943656 polymorphism between healthy controls and the sarcopenia group

	Genotype (%)					Allele (%)			
Group	**AA**	**AG**	**GG**	χ^2	p_1	**A**	**G**	χ^2	p_2
Sarcopenia	2 (2.5)	26 (32.5)	52 (65.0)	0.709	0.807	30 (18.75)	130 (81.25)	0.313	0.576
S-Male	1 (2.5)	14 (35.0)	25 (62.5)	2.175	0.328	16 (20.0)	64 (80.0)	0.040	0.841
S-Female	1 (2.5)	12 (30.0)	27 (67.5)	1.600	0.670	14 (17.5)	66 (82.5)	0.954	0.329
Control	4 (5.0)	26 (32.5)	50 (62.5)	—	—	34 (21.25)	126 (78.75)	—	—
C-Male	3 (7.5)	9 (22.5)	28 (70.0)	—	—	15 (18.75)	65 (81.25)	—	—
C-Female	1 (2.5)	17 (42.5)	22 (55.0)	—	—	19 (23.75)	61 (76.25)	—	—

2013; Loos & Yeo, 2014). According to Wang et al., (2017), the expression of PGC-1α and mitochondrial biogenesis with mTOR dependency is regulated by *FTO*, and skeletal muscle differentiation and development are influenced by the mTOR-PGC-1α-mitochondria axis. In skeletal muscle, *FTO* mRNA expression is negatively associated with lipid accumulation and positively correlated with glucose oxidation rates and the expression of genes involved in oxidative phosphorylation including PGC-1α (Grunnet et al., 2009; Wu et al., 2017). *FTO* mRNA abundance in skeletal muscle is significantly reduced in elderly subjects compared to younger ones (Grunnet et al., 2009). In the elderly, the decrease in *FTO* mRNA may reduce mTOR signaling, leading to impairment of skeletal muscle differentiation and development, and increasing autophagy; it may also reduce the expression of PGC-1α, impair mitochondrial function, accelerate muscle atrophy, increase lipid accumulation in skeletal muscle cells, and have a negative impact on muscle mass, leading to sarcopenia. According to Mehrdad et al. (2020), the *FTO* rs9939609 polymorphism is associated with serum levels of leptin, and the homozygotes for the *FTO* rs9939609 minor allele (A) have higher levels than the TT genotype. Appendicular skeletal muscle mass is negatively correlated with leptin, and compared to non-sarcopenic subjects, serum levels of leptin are significantly higher in sarcopenic patients (C. W. Li et al., 2019; Waters et al., 2008). The increase in leptin may play a key role in the development of age-related sarcopenia (Morley, 2001; Ng et al., 2018). Therefore, further investigation is needed to determine the association between *FTO* polymorphisms with serum levels of leptin in Tibetans.

TABLE 6 Association between *FTO* rs9939609 genotypes (TT, AT, & AA) and body composition and anthropometric indices

Male	Genotype (*n*)					Female	Genotype (*n*)				
Index	**TT (50)**	**AT (26)**	**AA (4)**	***F***	***p***	**Index**	**TT (41)**	**AT (35)**	**AA (4)**	***F***	***p***
Age	52.06 ± 7.62	53.31 ± 7.06	53.75 ± 7.89	0.294	0.746	Age	55.05 ± 8.55	53.11 ± 8.17	47.50 ± 5.80	1.739	0.183
Height (cm)	169.70 ± 7.36	166.52 ± 6.74	166.25 ± 2.63	1.965	0.147	Height (cm)	157.50 ± 5.49	158.59 ± 5.46	161.75 ± 2.06	1.306	0.277
Weight (kg)	63.73 ± 10.53	64.69 ± 10.46	60.10 ± 7.94	0.347	0.708	Weight (kg)	57.36 ± 9.29	62.11 ± 12.21	64.48 ± 8.78	2.278	0.109
BMI (kg/m^2)	22.10 ± 3.22	23.29 ± 3.42	21.78 ± 3.18	1.217	0.302	BMI (kg/m^2)	23.05±3.11	24.65 ± 4.60	24.68 ± 3.87	1.727	0.185
FFM (kg)	50.68 ± 6.34	50.47 ± 5.95	49.70 ± 3.55	0.051	0.950	FFM (kg)	38.92 ± 3.83	40.55 ± 4.09	41.95 ± 1.26	2.316	0.106
FM (kg)	13.09 ± 5.36	14.26 ± 5.90	10.40 ± 4.45	0.983	0.379	FM (kg)	18.44 ± 6.29	21.58 ± 9.11	22.55 ± 7.52	1.790	0.174
SMM (kg)	48.03 ± 6.02	47.85 ± 5.66	47.13 ± 3.39	0.048	0.953	SMM (kg)	36.69 ± 3.52	38.16 ± 3.74	39.43 ± 1.21	2.250	0.112
TSM (kg)	26.90±2.89	26.82 ± 3.00	26.18 ± 2.00	0.116	0.89	TSM (kg)	21.60 ± 1.86	22.04 ± 1.90	22.55 ± 0.37	0.871	0.423
LUSM (kg)	2.56 ± 0.41	2.58±0.36	2.58 ± 0.22	0.013	0.987	LUSM (kg)	1.79 ± 0.25	1.92 ± 0.29	1.93±0.26	2.218	0.116
LLSM (kg)	7.94 ± 1.25	7.89 ± 1.14	7.80 ± 0.98	0.035	0.965	LLSM (kg)	5.70 ± 0.72	6.07 ± 0.79	6.50 ± 0.62	3.731	0.028
RUSM (kg)	2.66 ± 0.42	2.66 ± 0.35	2.70 ± 0.22	0.020	0.980	RUSM (kg)	1.87 ± 0.27	2.01 ± 0.32	2.05 ± 0.26	2.448	0.093
RLSM (kg)	8.08 ± 1.28	8.02 ± 1.19	7.95 ± 0.73	0.032	0.969	RLSM (kg)	5.83 ± 0.68	6.23 ± 0.81	6.53 ± 0.25	3.788	0.027
TFM (kg)	7.61 ± 3.35	8.33 ± 3.73	5.78 ± 2.74	1.057	0.352	TFM (kg)	10.41 ± 4.15	12.24 ± 5.86	12.75 ± 4.38	1.443	0.242
LUFM (kg)	0.48 ± 0.23	0.51 ± 0.26	0.40 ± 0.18	0.439	0.646	LUFM (kg)	0.78 ± 0.37	1.00 ± 0.56	1.03 ± 0.54	2.154	0.123
LLFM (kg)	2.33 ± 0.82	2.52 ± 0.88	2.00 ± 0.65	0.881	0.419	LLFM (kg)	3.27 ± 0.76	3.69 ± 1.08	3.93 ± 1.09	2.456	0.092
RUFM (kg)	0.46 ± 0.21	0.49 ± 0.23	0.40 ± 0.18	0.415	0.662	RUFM (kg)	0.76 ± 0.37	0.97 ± 0.57	1.00 ± 0.55	2.026	0.139
RLFM (kg)	2.31 ± 0.84	2.50 ± 0.88	2.00 ± 0.68	0.820	0.444	RLFM (kg)	3.36 ± 0.77	3.80 ± 1.12	3.93 ± 0.97	2.353	0.102
HS (kg)	31.08 ± 7.62	31.82 ± 7.20	30.58 ± 15.31	0.092	0.912	HS (kg)	18.94 ± 6.74	19.84 ± 5.82	21.58 ± 7.65	0.419	0.659

Abbreviations: BMI, body mass index; FFM, fat-free mass; FM, fat mass; HS, handgrip strength; LLFM, left lower limb fat mass; LLSM, left lower limb skeletal muscle mass; LUFM, left upper limb fat mass; LUSM, left upper limb skeletal muscle mass; RLFM, right lower limb fat mass; RLSM, right lower limb skeletal muscle mass; RUFM, right upper limb fat mass; RUSM, right upper limb skeletal muscle mass; SMM, skeletal muscle mass; TFM, trunk fat mass; TSM, trunk skeletal muscle mass.

TABLE 7 Association between *FTO* rs9936385 genotypes (TT, CT, & CC) and body composition and anthropometric indices

Male	Genotype (*n*)					Female	Genotype (*n*)				
Index	**TT (50)**	**CT (26)**	**CC (4)**	***F***	***p***	**Index**	**TT (41)**	**CT (35)**	**CC (4)**	***F***	***p***
Age	52.06 ± 7.62	53.31 ± 7.06	53.75 ± 7.89	0.294	0.746	Age	55.05 ± 8.55	53.11 ± 8.17	47.50 ± 5.80	1.739	0.183
Height (cm)	169.70 ± 7.36	166.52 ± 6.74	166.25 ± 2.63	1.965	0.147	Height (cm)	157.50 ± 5.49	158.59 ± 5.46	161.75 ± 2.06	1.306	0.277
Weight (kg)	63.73 ± 10.53	64.69 ± 10.46	60.10 ± 7.94	0.347	0.708	Weight (kg)	57.36 ± 9.29	62.11 ± 12.21	64.48 ± 8.78	2.278	0.109
BMI (kg/m^2)	22.10 ± 3.22	23.29 ± 3.42	21.78 ± 3.18	1.217	0.302	BMI (kg/m^2)	23.05 ± 3.11	24.65 ± 4.60	24.68 ± 3.87	1.727	0.185
FFM (kg)	50.68 ± 6.34	50.47 ± 5.95	49.70 ± 3.55	0.051	0.950	FFM (kg)	38.92 ± 3.83	40.55 ± 4.09	41.95 ± 1.26	2.316	0.106
FM (kg)	13.09 ± 5.36	14.26 ± 5.90	10.40 ± 4.45	0.983	0.379	FM (kg)	18.44 ± 6.29	21.58 ± 9.11	22.55 ± 7.52	1.790	0.174
SMM (kg)	48.03 ± 6.02	47.85 ± 5.66	47.13 ± 3.39	0.048	0.953	SMM (kg)	36.69 ± 3.52	38.16 ± 3.74	39.43 ± 1.21	2.250	0.112
TSM (kg)	26.90 ± 2.89	26.82 ± 3.00	26.18 ± 2.00	0.116	0.89	TSM (kg)	21.60 ± 1.86	22.04 ± 1.90	22.55 ± 0.37	0.871	0.423
LUSM (kg)	2.56 ± 0.41	2.58 ± 0.36	2.58 ± 0.22	0.013	0.987	LUSM (kg)	1.79 ± 0.25	1.92 ± 0.29	1.93 ± 0.26	2.218	0.116
LLSM (kg)	7.94 ± 1.25	7.89 ± 1.14	7.80 ± 0.98	0.035	0.965	LLSM (kg)	5.70 ± 0.72	6.07 ± 0.79	6.50 ± 0.62	3.731	0.028
RUSM (kg)	2.66 ± 0.42	2.66 ± 0.35	2.70 ± 0.22	0.020	0.980	RUSM (kg)	1.87 ± 0.27	2.01 ± 0.32	2.05 ± 0.26	2.448	0.093
RLSM (kg)	8.08 ± 1.28	8.02 ± 1.19	7.95 ± 0.73	0.032	0.969	RLSM (kg)	5.83 ± 0.68	6.23 ± 0.81	6.53 ± 0.25	3.788	0.027
TFM (kg)	7.61 ± 3.35	8.33 ± 3.73	5.78 ± 2.74	1.057	0.352	TFM (kg)	10.41 ± 4.15	12.24 ± 5.86	12.75 ± 4.38	1.443	0.242
LUFM (kg)	0.48 ± 0.23	0.51 ± 0.26	0.40 ± 0.18	0.439	0.646	LUFM (kg)	0.78 ± 0.37	1.00 ± 0.56	1.03 ± 0.54	2.154	0.123
LLFM (kg)	2.33 ± 0.82	2.52 ± 0.88	2.00 ± 0.65	0.881	0.419	LLFM (kg)	3.27 ± 0.76	3.69 ± 1.08	3.93 ± 1.09	2.456	0.092
RUFM (kg)	0.46 ± 0.21	0.49 ± 0.23	0.40 ± 0.18	0.415	0.662	RUFM (kg)	0.76 ± 0.37	0.97 ± 0.57	1.00 ± 0.55	2.026	0.139
RLFM (kg)	2.31 ± 0.84	2.50 ± 0.88	2.00 ± 0.68	0.820	0.444	RLFM (kg)	3.36 ± 0.77	3.80 ± 1.12	3.93 ± 0.97	2.353	0.102
HS (kg)	31.08 ± 7.62	31.82 ± 7.20	30.58 ± 15.31	0.092	0.912	HS (kg)	18.94 ± 6.74	19.84 ± 5.82	21.58 ± 7.65	0.419	0.659

Abbreviations: BMI, body mass index; FFM, fat-free mass; FM, fat mass; HS, handgrip strength; LLFM, left lower limb fat mass; LLSM, left lower limb skeletal muscle mass; LUFM, left upper limb fat mass; LUSM, left upper limb skeletal muscle mass; RLFM, right lower limb fat mass; RLSM, right lower limb skeletal muscle mass; RUFM, right upper limb fat mass; RUSM, right upper limb skeletal muscle mass; SMM, skeletal muscle mass; TFM, trunk fat mass; TSM, trunk skeletal muscle mass.

TABLE 8 Association between *ACVR2B* rs2276541 genotypes (AA, AG, & GG) and body composition and anthropometric indices

Male	Genotype (*n*)					Female	Genotype (*n*)				
Index	**AA (24)**	**AG (38)**	**GG (18)**	***F***	***p***	**Index**	**AA (21)**	**AG (38)**	**GG (21)**	***F***	***p***
Age	50.00 ± 6.67	53.34 ± 7.47	54.28 ± 7.65	2.205	0.117	Age	52.29 ± 6.81	53.74 ± 9.57	55.52 ± 7.43	0.786	0.459
Height (cm)	168.92 ± 6.88	168.50 ± 7.70	167.92 ± 6.45	0.099	0.906	Height (cm)	158.76 ± 5.37	157.29 ± 5.50	159.24 ± 5.24	1.041	0.358
Weight (kg)	65.55 ± 12.51	63.17 ± 9.76	63.07 ± 8.43	0.453	0.638	Weight (kg)	59.08 ± 10.65	58.53 ± 11.84	62.80 ± 8.83	1.115	0.333
BMI (kg/m^2)	22.91 ± 3.83	22.24 ± 3.11	22.38 ± 3.01	0.311	0.734	BMI (kg/m^2)	23.41 ± 3.96	23.57 ± 4.29	24.71 ± 3.04	0.737	0.482
FFM (kg)	51.58 ± 6.46	50.31 ± 6.24	49.73 ± 5.18	0.534	0.588	FFM (kg)	39.86 ± 4.12	39.37 ± 4.04	40.48 ± 3.66	0.539	0.585
FM (kg)	14.00 ± 6.94	12.90 ± 4.97	13.36 ± 4.60	0.29	0.749	FM (kg)	19.23 ± 7.57	19.17 ± 8.72	22.34 ± 5.79	1.279	0.284
SMM (kg)	48.90 ± 6.12	47.68 ± 5.94	47.14 ± 4.92	0.535	0.588	SMM (kg)	37.53 ± 3.78	37.09 ± 3.70	38.10 ± 3.35	0.525	0.594
TSM (kg)	27.26 ± 2.92	26.55 ± 3.01	26.88 ± 2.52	0.447	0.641	TSM (kg)	21.84 ± 1.86	21.62 ± 1.81	22.22 ± 1.89	0.714	0.493
LUSM (kg)	2.62 ± 0.38	2.59 ± 0.42	2.45 ± 0.31	1.103	0.337	LUSM (kg)	1.87 ± 0.30	1.83 ± 0.27	1.89 ± 0.27	0.332	0.719
LLSM (kg)	8.13 ± 1.31	7.90 ± 1.21	7.67 ± 0.96	0.796	0.455	LLSM (kg)	5.94 ± 0.81	5.84 ± 0.81	5.96 ± 0.69	0.196	0.822
RUSM (kg)	2.71 ± 0.39	2.68 ± 0.43	2.56 ± 0.31	0.898	0.412	RUSM (kg)	1.95 ± 0.30	1.91 ± 0.30	1.98 ± 0.28	0.406	0.668
RLSM (kg)	8.28 ± 1.39	8.08 ± 1.18	7.69 ± 1.03	1.246	0.293	RLSM (kg)	6.04 ± 0.73	5.98 ± 0.79	6.14 ± 0.74	0.323	0.725
TFM (kg)	8.11 ± 4.21	7.44 ± 3.16	7.95 ± 3.10	0.306	0.737	TFM (kg)	10.70 ± 4.85	10.79 ± 5.67	12.94 ± 3.56	1.489	0.232
LUFM (kg)	0.51 ± 0.30	0.48 ± 0.22	0.46 ± 0.18	0.263	0.77	LUFM (kg)	0.86 ± 0.48	0.84 ± 0.53	1.01 ± 0.38	0.929	0.399
LLFM (kg)	2.51 ± 1.08	2.33 ± 0.74	2.29 ± 0.61	0.455	0.636	LLFM (kg)	3.45 ± 0.93	3.38 ± 1.03	3.72 ± 0.78	0.885	0.417
RUFM (kg)	0.49 ± 0.28	0.46 ± 0.19	0.46 ± 0.16	0.17	0.844	RUFM (kg)	0.83 ± 0.49	0.82 ± 0.53	0.98 ± 0.37	0.791	0.457
RLFM (kg)	2.50 ± 1.09	2.29 ± 0.77	2.31 ± 0.61	0.476	0.623	RLFM (kg)	3.52 ± 0.93	3.47 ± 1.05	3.83 ± 0.81	1.011	0.369
HS (kg)	32.61 ± 7.96	30.45 ± 8.35	31.32 ± 6.64	0.555	0.577	HS (kg)	19.80 ± 5.62	19.78 ± 6.95	18.55 ± 6.06	0.289	0.750

Abbreviations: BMI, body mass index; FFM, fat-free mass; FM, fat mass; HS, handgrip strength; LLFM, left lower limb fat mass; LLSM, left lower limb skeletal muscle mass; LUFM, left upper limb fat mass; LUSM, left upper limb skeletal muscle mass; RLFM, right lower limb fat mass; RLSM, right lower limb skeletal muscle mass; RUFM, right upper limb fat mass; RUSM, right upper limb skeletal muscle mass; SMM, skeletal muscle mass; TFM, trunk fat mass; TSM, trunk skeletal muscle mass.

TABLE 9 Association between *IRS1* rs2943656 genotypes (AA, AG, & GG) and body composition and anthropometric indices

Male	Genotype (*n*)					Female	Genotype (*n*)				
Index	**AA (4)**	**AG (23)**	**GG (53)**	***F***	***p***	**Index**	**AA (2)**	**AG (29)**	**GG (49)**	***F***	***p***
Age	53.25 ± 7.46	50.48 ± 6.81	53.40 ± 7.58	1.278	0.284	Age	55.00 ± 14.14	52.79 ± 7.82	54.39 ± 8.63	0.345	0.709
Height (cm)	167.75 ± 3.50	170.37 ± 7.71	167.74 ± 7.00	1.125	0.330	Height (cm)	154.50 ± 3.54	159.19 ± 4.49	157.74 ± 5.89	1.133	0.328
Weight (kg)	72.83 ± 14.58	63.24 ± 10.21	63.45 ± 9.96	1.614	0.206	Weight (kg)	59.70 ± 20.51	62.56 ± 10.99	58.16 ± 10.33	1.524	0.224
BMI (kg/m^2)	25.95 ± 5.36	21.76 ± 3.09	22.52 ± 3.10	2.911	0.060	BMI (kg/m^2)	24.80 ± 7.50	24.64 ± 3.97	23.31 ± 3.74	1.127	0.329
FFM (kg)	53.83 ± 3.82	50.15 ± 6.30	50.49 ± 6.09	0.632	0.535	FFM (kg)	37.95 ± 5.87	40.58 ± 4.04	39.40 ± 3.83	1.040	0.358
FM (kg)	19.03 ± 11.05	13.13 ± 4.81	12.99 ± 5.16	2.328	0.104	FM (kg)	21.80 ± 14.71	22.00 ± 7.65	18.78 ± 7.55	1.640	0.201
SMM (kg)	51.05 ± 3.65	47.53 ± 5.98	47.86 ± 5.79	0.641	0.530	SMM (kg)	35.80 ± 5.37	38.19 ± 3.71	37.11 ± 3.50	1.028	0.363
TSM (kg)	28.30 ± 0.48	26.58 ± 2.96	26.84 ± 2.92	0.608	0.547	TSM (kg)	20.50 ± 1.13	21.98 ± 1.69	21.81 ± 1.94	0.614	0.544
LUSM (kg)	2.80 ± 0.26	2.53 ± 0.41	2.57 ± 0.38	0.850	0.431	LUSM (kg)	1.85 ± 0.49	1.92 ± 0.31	1.81 ± 0.24	1.465	0.237
LLSM (kg)	8.53 ± 1.45	7.90 ± 1.21	7.88 ± 1.17	0.550	0.579	LLSM (kg)	5.65 ± 1.63	6.09 ± 0.86	5.80 ± 0.67	1.443	0.243
RUSM (kg)	2.85 ± 0.30	2.61 ± 0.41	2.67 ± 0.39	0.650	0.525	RUSM (kg)	1.95 ± 0.49	2.01 ± 0.33	1.90 ± 0.26	1.478	0.234
RLSM (kg)	8.68 ± 1.54	8.01 ± 1.33	8.02 ± 1.16	0.540	0.585	RLSM (kg)	5.90 ± 1.56	6.28 ± 0.80	5.90 ± 0.68	2.408	0.097
TFM (kg)	11.23 ± 6.80	7.64 ± 2.97	7.54 ± 3.29	2.187	0.119	TFM (kg)	12.15 ± 8.56	12.46 ± 4.79	10.63 ± 5.02	1.247	0.293
LUFM (kg)	0.73 ± 0.50	0.47 ± 0.20	0.47 ± 0.22	2.247	0.113	LUFM (kg)	1.10 ± 0.99	1.02 ± 0.49	0.80 ± 0.44	2.187	0.119
LLFM (kg)	3.28 ± 1.68	2.33 ± 0.76	2.32 ± 0.76	2.590	0.082	LLFM (kg)	3.75 ± 2.05	3.78 ± 0.98	3.30 ± 0.85	2.471	0.091
RUFM (kg)	0.70 ± 0.45	0.47 ± 0.19	0.45 ± 0.19	2.665	0.076	RUFM (kg)	1.05 ± 0.92	1.00 ± 0.50	0.78 ± 0.44	1.980	0.145
RLFM (kg)	3.28 ± 1.68	2.33 ± 0.75	2.30 ± 0.78	2.592	0.081	RLFM (kg)	3.90 ± 2.12	3.87 ± 1.00	3.39 ± 0.87	2.411	0.096
HS (kg)	39.68 ± 9.17	30.93 ± 7.74	30.82 ± 7.58	2.499	0.089	HS (kg)	21.55 ± 9.55	19.89 ± 7.60	19.13 ± 5.49	0.238	0.788

Abbreviations: BMI, body mass index; FFM, fat-free mass; FM, fat mass; HS, handgrip strength; LLFM, left lower limb fat mass; LLSM, left lower limb skeletal muscle mass; LUFM, left upper limb fat mass; LUSM, left upper limb skeletal muscle mass; RLFM, right lower limb fat mass; RLSM, right lower limb skeletal muscle mass; RUFM, right upper limb fat mass; RUSM, right upper limb skeletal muscle mass; SMM, skeletal muscle mass; TFM, trunk fat mass; TSM, trunk skeletal muscle mass.

TABLE 10 Comparison of *FTO* rs9939609 polymorphism among different populations

Group	Reference	*n*	TT	AT	AA	A	T
Tibetan (Control)	—	80	37 (46.25)	38 (47.5)	5 (6.25)	48 (30.0)	112(70.0)
Tibetan (Sarcopenia)	—	80	54 (67.5)	23 (28.75)	3 (3.75)	29 (18.1)	131 (81.9)
Han (Hubei)	Huang et al., (2011)	1200	450 (37.5)	545 (45.4)	205 (17.1)	955 (39.8)	1445 (60.2)
Mongolians	Zhang et al., (2018)	200	156 (78.0)	40 (20.0)	4 (2.0)	48 (12.0)	352 (88.0)
Taiwanese	Chang et al. (2008)	1525	1158 (75.9)	347 (22.8)	20 (1.3)	387 (12.7)	2663 (87.3)
Kazakh	Sikhayeva et al. (2017)	767	436 (56.8)	274 (35.7)	57 (7.4)	388 (25.3)	1146 (74.7)
Mexican	Villalobos-Comparán et al., (2008)	424	297 (70.0)	114 (26.9)	13 (3.1)	140 (16.5)	708 (83.5)
Russian	Guilherme et al. (2019)	754	320 (42.4)	333 (44.2)	101 (13.4)	535 (35.5)	973 (64.5)
Brazilian	Guilherme et al. (2019)	652	261 (40.0)	297 (45.6)	94 (14.4)	485 (37.2)	819 (62.8)
Indian	Ningombam et al. (2018)	521	381 (73.1)	138 (26.5)	2 (0.4)	142 (13.6)	900 (86.4)
Swede	Gustavsson et al. (2014)	4402	1629 (37.0)	2066 (46.9)	707 (16.1)	3480 (39.5)	5324 (60.5)
Japanese	Karasawa et al. (2010)	2639	1680 (63.7)	837 (31.7)	122 (4.6)	1081 (20.5)	4197 (79.5)
Turkish	Ağagündüz and Gezmen-Karadağ (2019)	200	77 (38.5)	85 (42.5)	38 (19.0)	161 (40.2)	239 (59.8)

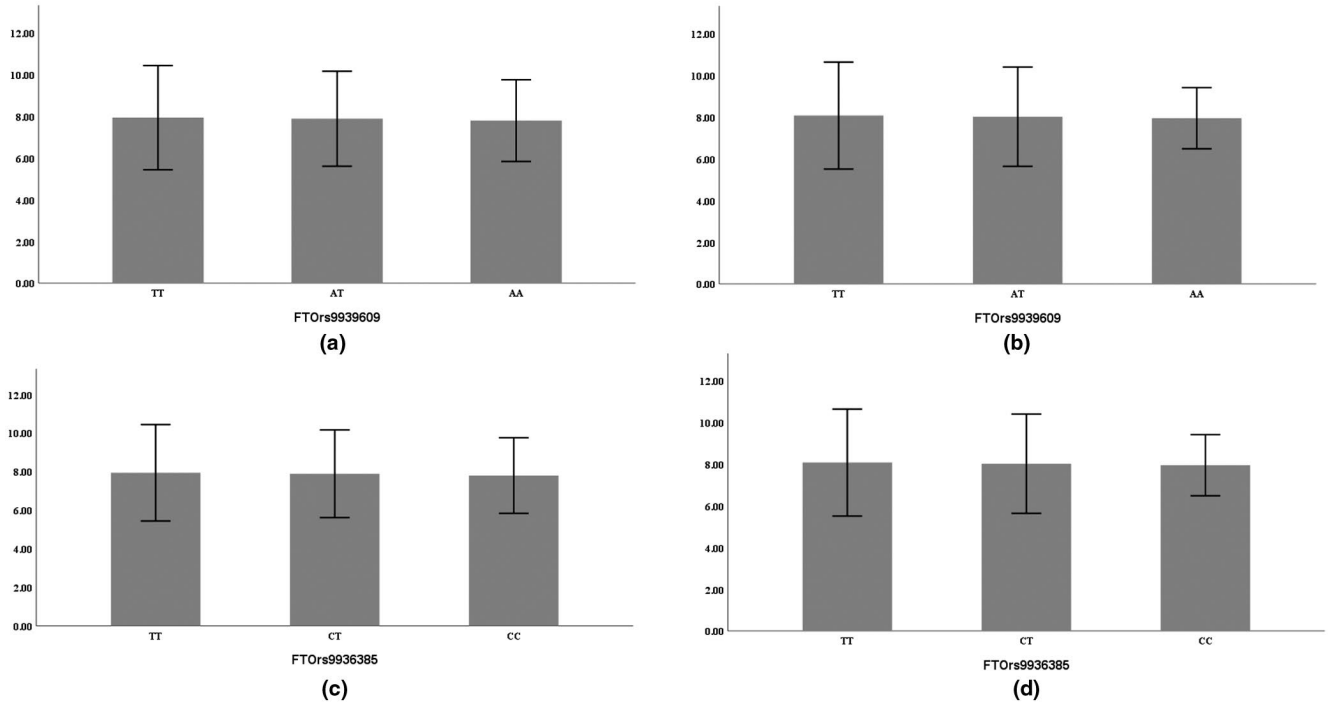

FIGURE 2 Comparison of the lower limb muscle mass (in men) among three genotypes (a,c: left lower limb, b,d: right lower limb, mean ± SD)

Previous studies have reported that the polymorphisms of *ACVR2B* rs2276541 and *IRS1* rs2943656 were associated with lean mass, but we found there was no association between polymorphisms of *ACVR2B* rs2276541 and *IRS1* rs2943656 and sarcopenia and body composition in Tibetans, it may be attributed to genetic differences. This proves that the identified risk genes cannot be applied to all populations. Both *ACVR2B* and *IRS1* code for a receptor, and further investigation is needed to research the association between polymorphisms of upstream gene (*MSTN*, *IGF1*) and sarcopenia in Tibetans. Interestingly, we found that the rs9939609 polymorphism was associated with the rs9936385 polymorphism in Tibetans. The A allele at rs9939609 and C allele at rs9936385 appeared concurrently, and further investigation is needed to determine the relationship between the two SNPs. And the previous study has found that the *FTO* mRNA level correlated positively with gene expression levels of hypoxia-inducible factor-1a(HIF-1a) related to hypoxia in adipose

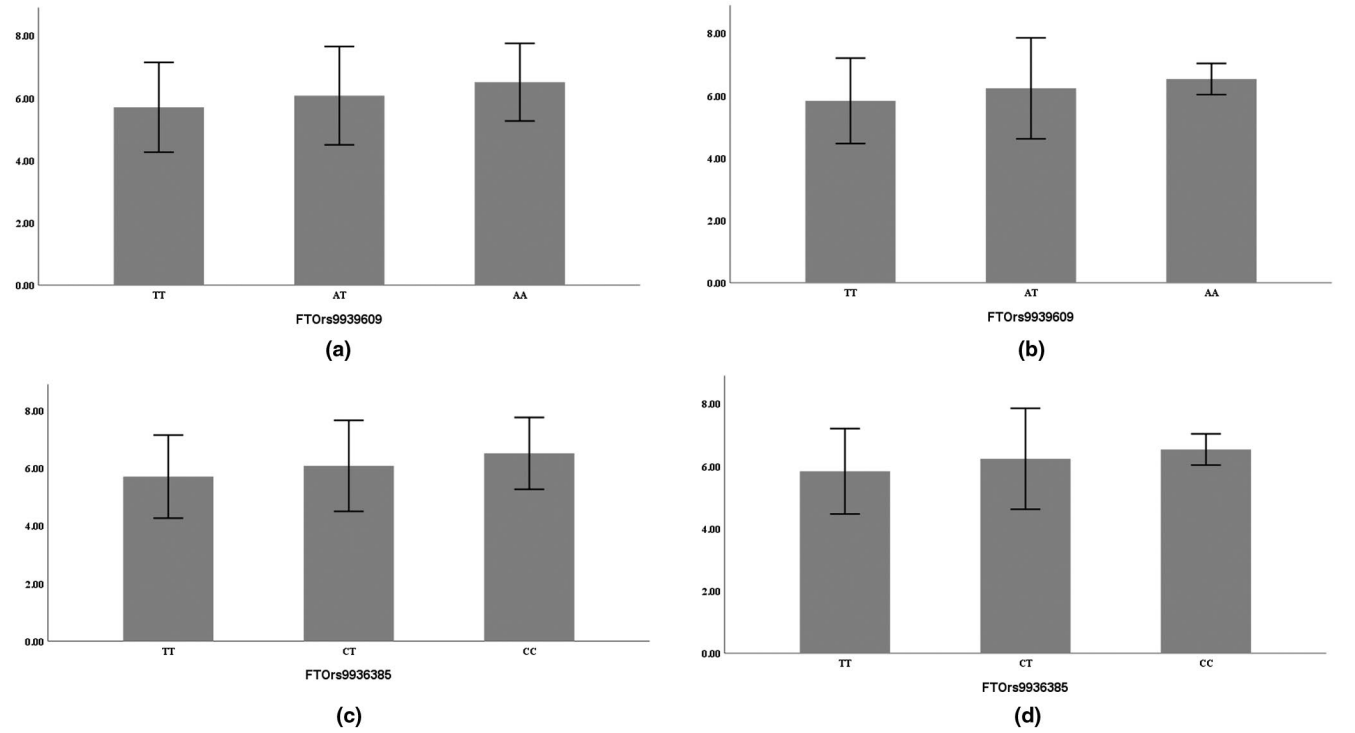

FIGURE 3 Comparison of lower limb muscle mass (in women) among three genotypes (a,c: left lower limb, b,d: right lower limb, mean ± SD)

tissue (Lappalainen et al., 2010). We speculate that the simultaneous mutation of the two SNPs in Tibetan people was caused by long-term exposure to the plateau environment, and it may have a protective effect on their skeletal muscle mass. The main limitation of our study was the limited sample size, which may have led to a certain deviation in the association between sarcopenia and gene polymorphisms.

5 | CONCLUSION

To the best of our knowledge, this is the first study to investigate the association between *FTO* rs9939609, *FTO* rs9936385, *ACVR2B* rs2276541, and *IRS1* rs2943656 polymorphisms with sarcopenia in the Tibetan population. Our study provides evidence for an association between *FTO* polymorphisms and lower limb muscle mass and sarcopenia in Tibetan women, TT homozygotes had a higher risk for sarcopenia. And we found there is no association between polymorphisms of *ACVR2B* rs2276541, *IRS1* rs2943656 and sarcopenia and body composition in Tibetans.

ACKNOWLEDGMENTS

We are grateful to the Lhasa Tama Community Health Service Center for their help.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICS STATEMENT

The study was approved by the Research Ethics Committee of Jinzhou Medical University in accordance with the Declaration of Helsinki. Verbal and written informed consent were obtained from all participants.

AUTHOR CONTRIBUTIONS

Xin Li, Ying Chen, Yaqiong Jiang, and Wenhui Li carried out the investigation of the Tibetan population. Liping Ye guided and helped perform the experiments. Youfeng Wen guided the investigation, and modified and reviewed the manuscript. Xianpeng Zhang carried out the experiments, and conceived and wrote the manuscript. All authors contributed to the article and approved the submitted version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ORCID

Xianpeng Zhang https://orcid.org/0000-0003-2145-4223

REFERENCES

Beall, C. M., Cavalleri, G. L., Deng, L., Elston, R. C., Gao, Y., Knight, J., Li, C., Li, J. C., Liang, Y., McCormack, M., Montgomery, H. E., Pan, H., Robbins, P. A., Shianna, K. V., Tam, S. C., Tsering, N., Veeramah, K. R., Wang, W., Wangdui, P., … Zheng, Y. T. (2010). Natural selection on EPAS1 (HIF2) associated with low

hemoglobin concentration in Tibetan highlanders. *Proceedings of the National Academy of Sciences*, *107*(25), 11459–11464. https://doi.org/10.1073/pnas.1002443107

Chen, L.-K., Liu, L.-K., Woo, J., Assantachai, P., Auyeung, T.-W., Bahyah, K. S., Chou, M.-Y., Chen, L.-Y., Hsu, P.-S., Krairit, O., Lee, J. S. W., Lee, W.-J., Lee, Y., Liang, C.-K., Limpawattana, P., Lin, C.-S., Peng, L.-N., Satake, S., Suzuki, T., … Arai, H. (2014). Sarcopenia in Asia: Consensus report of the Asian Working Group for Sarcopenia. *Journal of the American Medical Directors Association*, *15*(2), 95–101. https://doi.org/10.1016/j.jamda.2013.11.025

Doaei, S., Kalantari, N., Mohammadi, N. K., Izadi, P., Gholamalizadeh, M., Eini-Zinab, H., Salonurmi, T., Jarrahi, A., Rafieifar, S., Janipoor, R., Sadeghypor, M., Tabesh, G., & Goodarzi, M. (2019). Up-regulation of FTO gene expression was associated with increase in skeletal muscle mass in overweight male adolescents. *Archives of Medical Science*, *15*(5), 1133–1137. https://doi.org/10.5114/aoms.2019.87239

Dünnwald, T., Gatterer, H., Faulhaber, M., Arvandi, M., & Schobersberger, W. (2019). Body composition and body weight changes at different altitude levels: A systematic review and meta-analysis. *Frontiers in Physiology*, *10*. https://doi.org/10.3389/fphys.2019.00430

Eltzschig, H. K., & Carmeliet, P. (2011). Hypoxia and inflammation. *New England Journal of Medicine*, *364*(7), 656–665. https://doi.org/10.1056/NEJMra0910283

Fusch, C., Gfrorer, W., Koch, C., Thomas, A., Grunert, A., & Moeller, H. (1996). Water turnover and body composition during long-term exposure to high altitude (4,900-7,600 m). *Journal of Applied Physiology*, *80*(4), 1118–1125. https://doi.org/10.1152/jappl.1996.80.4.1118

Grant, S. F. A., Li, M., Bradfield, J. P., Kim, C. E., Annaiah, K., Santa, E., Glessner, J. T., Casalunovo, T., Frackelton, E. C., Otieno, F. G., Shaner, J. L., Smith, R. M., Imielinski, M., Eckert, A. W., Chiavacci, R. M., Berkowitz, R. I., & Hakonarson, H. (2008). Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. *PLoS One*, *3*(3), e1746. https://doi.org/10.1371/journal.pone.0001746

Grunnet, L. G., Nilsson, E., Ling, C., Hansen, T., Pedersen, O., Groop, L., Vaag, A., & Poulsen, P. (2009). Regulation and function of FTO mRNA expression in human skeletal muscle and subcutaneous adipose tissue. *Diabetes*, *58*(10), 2402–2408. https://doi.org/10.2337/db09-0205

Gulati, P., Cheung, M. K., Antrobus, R., Church, C. D., Harding, H. P., Tung, Y.-C.- L., Rimmington, D., Ma, M., Ron, D., Lehner, P. J., Ashcroft, F. M., Cox, R. D., Coll, A. P., O'Rahilly, S., & Yeo, G. S. H. (2013). Role for the obesity-related FTO gene in the cellular sensing of amino acids. *Proceedings of the National Academy of Sciences*, *110*(7), 2557–2562. https://doi.org/10.1073/pnas.1222796110

Heffernan, S. M., Stebbings, G. K., Kilduff, L. P., Erskine, R. M., Day, S. H., Morse, C. I., McPhee, J. S., Cook, C. J., Vance, B., Ribbans, W. J., Raleigh, S. M., Roberts, C., Bennett, M. A., Wang, G., Collins, M., Pitsiladis, Y. P., & Williams, A. G. (2017). Fat mass and obesity associated (FTO) gene influences skeletal muscle phenotypes in non-resistance trained males and elite rugby playing position. *BMC Genetics*, *18*(1). https://doi.org/10.1186/s12863-017-0470-1

Hinney, A., Nguyen, T. T., Scherag, A., Friedel, S., Brönner, G., Müller, T. D., Grallert, H., Illig, T., Wichmann, H.-E., Rief, W., Schäfer, H., & Hebebrand, J. (2007). Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. *PLoS One*, *2*(12), e1361. https://doi.org/10.1371/journal.pone.0001361

Huang, W., Sun, Y., & Sun, J. (2011). Combined effects of FTO rs9939609 and MC4R rs17782313 on obesity and BMI in Chinese Han populations. *Endocrine*, *39*(1), 69–74. https://doi.org/10.1007/s12020-010-9413-6

Karasik, D., Zillikens, M. C., Hsu, Y.-H., Aghdassi, A., Akesson, K., Amin, N., Barroso, I., Bennett, D. A., Bertram, L., Bochud, M., Borecki, I. B., Broer, L., Buchman, A. S., Byberg, L., Campbell, H., Campos-Obando, N., Cauley, J. A., Cawthon, P. M., Chambers, J. C., … Ohlsson, C. (2019). Disentangling the genetics of lean mass. *The American Journal of Clinical Nutrition*, *109*(2), 276–287. https://doi.org/10.1093/ajcn/nqy272

Khanal, P., He, L., Stebbings, G., Onambele-Pearson, G. L., Degens, H., Williams, A., Thomis, M., & Morse, C. I. (2020). Prevalence and association of single nucleotide polymorphisms with sarcopenia in older women depends on definition. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-59722-9

Klimentidis, Y. C., Bea, J. W., Thompson, P., Klimecki, W. T., Hu, C., Wu, G., Nicholas, J. S., Ryckman, K. K., & Chen, Z. (2016). Genetic variant in ACVR2B is associated with lean mass. *Medicine & Science in Sports & Exercise*, *48*(7), 1270–1275. https://doi.org/10.1249/mss.0000000000000889

Lappalainen, T., Kolehmainen, M., Schwab, U., Pulkkinen, L., de Mello, V. D. F., Vaittinen, M., Laaksonen, D. E., Poutanen, K., Uusitupa, M., & Gylling, H. (2010). Gene expression of FTO in human subcutaneous adipose tissue, peripheral blood mononuclear cells and adipocyte cell line. *Journal of Nutrigenetics and Nutrigenomics*, *3*(1), 37–45. https://doi.org/10.1159/000320732

Lee, S.-J., & McPherron, A. C. (2001). Regulation of myostatin activity and muscle growth. *Proceedings of the National Academy of Sciences*, *98*(16), 9306–9311. https://doi.org/10.1073/pnas.151270098

Li, C.-W., Yu, K., Shyh-Chang, N. G., Li, G.-X., Jiang, L.-J., Yu, S.-L., Xu, L.-Y., Liu, R.-J., Guo, Z.-J., Xie, H.-Y., Li, R.-R., Ying, J., Li, K., & Li, D.-J. (2019). Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention. *Journal of Cachexia, Sarcopenia and Muscle*, *10*(3), 586–600. https://doi.org/10.1002/jcsm.12417

Li, Z., Cai, B., Abdalla, B. A., Zhu, X., Zheng, M., Han, P., & Zhang, X. (2019). LncIRS1 controls muscle atrophy via sponging miR-15 family to activate IGF1-PI3K/AKT pathway. *Journal of Cachexia, Sarcopenia and Muscle*, *10*(2), 391–410. https://doi.org/10.1002/jcsm.12374

Livshits, G., Malkin, I., Moayyeri, A., Spector, T. D., & Hammond, C. J. (2012). Association of FTO gene variants with body composition in UK twins. *Annals of Human Genetics*, *76*(5), 333–341. https://doi.org/10.1111/j.1469-1809.2012.00720.x

Loos, R. J. F., & Yeo, G. S. H.(2014). The bigger picture of FTO—The first GWAS-identified obesity gene. *Nature Reviews Endocrinology*, *10*(1), 51–61. https://doi.org/10.1038/nrendo.2013.227

Lu, D., Lou, H., Yuan, K., Wang, X., Wang, Y., Zhang, C., Lu, Y., Yang, X., Deng, L., Zhou, Y., Feng, Q., Hu, Y. A., Ding, Q., Yang, Y., Li, S., Jin, L. I., Guan, Y., Su, B., Kang, L., & Xu, S. (2016). Ancestral origins and genetic history of Tibetan highlanders. *The American Journal of Human Genetics*, *99*(3), 580–594. https://doi.org/10.1016/j.ajhg.2016.07.002

McGarry, T., Biniecka, M., Veale, D. J., & Fearon, U. (2018). Hypoxia, oxidative stress and inflammation. *Free Radical Biology and*

Medicine, *125*, 15–24. https://doi.org/10.1016/j.freeradbiomed.2018.03.042

McMurray, F., Church, C. D., Larder, R., Nicholson, G., Wells, S., Teboul, L., Tung, Y. C. L., Rimmington, D., Bosch, F., Jimenez, V., Yeo, G. S. H., O'Rahilly, S., Ashcroft, F. M., Coll, A. P., & Cox, R. D. (2013). Adult onset global loss of the Fto gene alters body composition and metabolism in the mouse. *PLoS Genetics*, *9*(1), e1003166. https://doi.org/10.1371/journal.pgen.1003166

Mehrdad, M., Doaei, S., Gholamalizadeh, M., Fardaei, M., Fararouei, M., & Eftekhari, M. H. (2020). Association of FTO rs9939609 polymorphism with serum leptin, insulin, adiponectin, and lipid profile in overweight adults. *Adipocyte*, *9*(1), 51–56. https://doi.org/10.1080/21623945.2020.1722550.

Merra, G., Gualtieri, P., Cioccoloni, G., Falco, S., Bigioni, G., Tarsitano, M. G., Capacci, A., Piccioni, A., Costacurta, M., Franceschi, F., & Di Renzo, L. (2020). FTO rs9939609 influence on adipose tissue localization in the Italian population. *European Review for Medical and Pharmacological Sciences*, *24*(6), 3223–3235. https://doi.org/10.26355/eurrev_202003_20689

Morley John, E. (2001). Anorexia, sarcopenia, and aging. *Nutrition*, *17*(7–8), 660–663. https://doi.org/10.1016/s0899-9007(01)00574-3

Ng, T. P., Lu, Y., Choo, R. W. M., Tan, C. T. Y., Nyunt, M. S. Z., Gao, Q. I., Mok, E. W. H., & Larbi, A. (2018). Dysregulated homeostatic pathways in sarcopenia among frail older adults. *Aging Cell*, *17*(6), e12842. https://doi.org/10.1111/acel.12842

Pasiakos, S. M., Berryman, C. E., Carrigan, C. T., Young, A. J., & Carbone, J. W. (2017). Muscle protein turnover and the molecular regulation of muscle mass during hypoxia. *Medicine & Science in Sports & Exercise*, *49*(7), 1340–1350. https://doi.org/10.1249/mss.0000000000001228

Pratt, J., Boreham, C., Ennis, S., Ryan, A. W., & De Vito, G. (2019). Genetic associations with aging muscle: A systematic review. *Cells*, *9*(1), 12–https://doi.org/10.3390/cells9010012

Ran, S., Jiang, Z.-X., He, X., Liu, Y. U., Zhang, Y.-X., Zhang, L., Pei, Y.-F., Zhang, M., Hai, R., Gu, G.-S., Liu, B.-L., Tian, Q., Zhang, Y.-H., Wang, J.-Y., & Deng, H.-W. (2020). Replication of FTO Gene associated with lean mass in a Meta-Analysis of Genome-Wide Association Studies. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-61406-3

Roth, S. M., Zmuda, J. M., Cauley, J. A., Shea, P. R., & Ferrell, R. E. (2004). Vitamin D receptor genotype is associated with fat-free mass and sarcopenia in elderly men. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *59*(1), B10–B15. https://doi.org/10.1093/gerona/59.1.b10

Sällman Almén, M., Rask-Andersen, M., Jacobsson, J. A., Ameur, A., Kalnina, I., Moschonis, G., Juhlin, S., Bringeland, N., Hedberg, L. A., Ignatovica, V., Chrousos, G. P., Manios, Y., Klovins, J., Marcus, C., Gyllensten, U., Fredriksson, R., & Schiöth, H. B. (2013). Determination of the obesity-associated gene variants within the entire FTO gene by ultra-deep targeted sequencing in obese and lean children. *International Journal of Obesity*, *37*(3), 424–431. https://doi.org/10.1038/ijo.2012.57

Shi, J., Luo, L., Eash, J., Ibebunjo, C., & Glass, D. J. (2011). The SCF-Fbxo40 complex induces IRS1 ubiquitination in skeletal muscle, limiting IGF1 signaling. *Developmental Cell*, *21*(5), 835–847. https://doi.org/10.1016/j.devcel.2011.09.011

Simonson, T. S., Yang, Y., Huff, C. D., Yun, H., Qin, G., Witherspoon, D. J., Bai, Z., Lorenzo, F. R., Xing, J., Jorde, L. B., Prchal, J. T., & Ge, R. (2010). Genetic evidence for high-altitude adaptation in Tibet. *Science*, *329*(5987), 72–75. https://doi.org/10.1126/science.1189406

Sonestedt, E., Gullberg, B., Ericson, U., Wirfält, E., Hedblad, B., & Orho-Melander, M. (2011). Association between fat intake, physical activity and mortality depending on genetic variation in FTO. *International Journal of Obesity*, *35*(8), 1041–1049. https://doi.org/10.1038/ijo.2010.263

Song, D., Navalsky, B. E., Guan, W., Ingersoll, C., Wang, T., Loro, E., Eeles, L., Matchett, K. B., Percy, M. J., Walsby-Tickle, J., McCullagh, J. S. O., Medina, R. J., Khurana, T. S., Bigham, A. W., Lappin, T. R., & Lee, F. S. (2020). TibetanPHD2, an allele with loss-of-function properties. *Proceedings of the National Academy of Sciences*, *117*(22), 12230–12238. https://doi.org/10.1073/pnas.1920546117

Tan, L. J., Liu, S. L., Lei, S. F., Papasian, C. J., & Deng, H. W. (2012). Molecular genetic studies of gene identification for sarcopenia. *Human Genetics*, *131*(1), 1–31. https://doi.org/10.1007/s00439-011-1040-7

Villalobos-Comparán, M., Teresa Flores-Dorantes, M., Teresa Villarreal-Molina, M., Rodríguez-Cruz, M., García-Ulloa, A. C., Robles, L., & Canizales-Quinteros, S. (2008). The FTO gene is associated with adulthood obesity in the Mexican population. *Obesity (Silver Spring)*, *16*(10), 2296–2301. https://doi.org/10.1038/oby.2008.367

Walsh, S., Metter, E. J., Ferrucci, L., & Roth, S. M. (2007). Activin type II receptor B (ACVR2B) and follistatin haplotype associations with muscle mass and strength in humans. *Journal of Applied Physiology*, *102*(6), 2142–2148. https://doi.org/10.1152/japplphysiol.01322.2006

Wandrag, L., Siervo, M., Riley, H. L., Khosravi, M., Fernandez, B. O., Leckstrom, C. A., Martin, D. S., Mitchell, K., Levett, D. Z. H., Montgomery, H. E., Mythen, M. G., Stroud, M. A., Grocott, M. P. W., & Feelisch, M. (2017). Does hypoxia play a role in the development of sarcopenia in humans? Mechanistic insights from the Caudwell Xtreme Everest Expedition. *Redox Biology*, *13*, 60–68. https://doi.org/10.1016/j.redox.2017.05.004

Wang, X., Huang, N., Yang, M., Wei, D., Tai, H., Han, X., Gong, H., Zhou, J., Qin, J., Wei, X., Chen, H., Fang, T., & Xiao, H. (2017). FTO is required for myogenesis by positively regulating mTOR-PGC-1α pathway-mediated mitochondria biogenesis. *Cell Death & Disease*, *8*(3), e2702. https://doi.org/10.1038/cddis.2017.122

Waters, D. L., Qualls, C. R., Dorin, R. I., Veldhuis, J. D., & Baumgartner, R. N. (2008). Altered growth hormone, cortisol, and leptin secretion in healthy elderly persons with sarcopenia and mixed body composition phenotypes. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *63*(5), 536–541. https://doi.org/10.1093/gerona/63.5.536

White, T. A., & LeBrasseur, N. K. (2014). Myostatin and sarcopenia: Opportunities and challenges - A mini-review. *Gerontology*, *60*(4), 289–293. https://doi.org/10.1159/000356740

Wing, M. R., Ziegler, J., Langefeld, C. D., Ng, M. C. Y., Haffner, S. M., Norris, J. M., Goodarzi, M. O., & Bowden, D. W. (2009). Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study. *Human Genetics*, *125*(5–6), 615–626. https://doi.org/10.1007/s00439-009-0656-3

Wu, W., Feng, J., Jiang, D., Zhou, X., Jiang, Q., Cai, M., Wang, X., Shan, T., & Wang, Y. (2017). AMPK regulates lipid accumulation in skeletal muscle cells through FTO-dependent demethylation of N6-methyladenosine. *Scientific Reports*, *7*(1). https://doi.org/10.1038/srep41606

Ye, L., Wen, Y., Chen, Y., Yao, J., Li, X., Liu, Y., Song, J., & Sun, Z. (2020). Diagnostic reference values for sarcopenia in Tibetans in China. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-60027-0

Zhang, Q., Xia, X., Fang, S., & Yuan, X. (2018). Relationship between fat mass and obesity-associated (FTO) gene polymorphisms with obesity and metabolic syndrome in ethnic Mongolians. *Medical Science Monitor*, *24*, 8232–8238. https://doi.org/10.12659/msm.910928

Zillikens, M. C., Demissie, S., Hsu, Y. H., Yerges-Armstrong, L. M., Chou, W. C., Stolk, L., Livshits, G., Broer, L., Johnson, T., Koller, D. L., Kutalik, Z., Luan, J., Malkin, I., Ried, J. S., Smith, A. V., Thorleifsson, G., Vandenput, L., Hua Zhao, J., Zhang, W., … Kiel, D. P. (2017). Large meta-analysis of genome-wide association studies identifies five loci for lean body mass. *Nature Communications*, *8*(1), 1–3. https://doi.org/10.1038/s41467-017-00031-7

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

How to cite this article: Zhang, X., Ye, L., Li, X., Chen, Y., Jiang, Y., Li, W., & Wen, Y. (2021). The association between sarcopenia susceptibility and polymorphisms of *FTO*, *ACVR2B*, and *IRS1* in Tibetans. *Molecular Genetics & Genomic Medicine*, 9, e1747. https://doi.org/10.1002/mgg3.1747