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The Q223R polymorphism in the *leptin receptor* associates with objectively measured light physical activity in free-living Japanese

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HIGHLIGHTS

- There were significant differences between *LEPR* genotypes and physical activity.
- RR genotype showed significantly shorter time spent in light PA.
- RR genotype showed significantly longer inactive time.

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ABSTRACT

Physical activity (PA) is associated with reductions in the risk of all-cause mortality and in the prevalence of cardiovascular disease and stroke. Nevertheless, a large proportion of the general population may not be sufficiently active. PA level has been reported to be influenced by genetic factors, and we investigated whether Q223R polymorphism in the *leptin receptor* (*LEPR*) gene was associated with PA level. A total of 556 Japanese adults aged 24–65 years old participated in this cross-sectional study. The duration and intensity of PA were objectively evaluated by triaxial accelerometry. Q223R polymorphism was determined by the TaqMan method. The distribution of Q223R polymorphism was: QQ 0.7%, QR 22.6%, and RR 76.6%. The relation between the *LEPR* genotype and PA level was analyzed by ANCOVA with age and sex as covariates in the Q dominant genetic model. There were significant differences between *LEPR* genotypes and the time spent in light PA or inactive time. The subjects with RR genotype showed significantly shorter time spent in light PA (RR genotype: 559.4 ± 102.9 min/day, QQ/QR genotype: 579.9 ± 103.1 min/day) and longer inactive time (RR genotype: 815.5 ± 107.5 min/day, QQ/QR genotype: 792.3 ± 107.7 min/day) than the subjects with QQ/QR genotype ($P < 0.05$). There were no such differences in the time spent in moderate or vigorous PA. These results suggest that the variety of PA level, especially spontaneous PA in humans, is partly caused by diversity in the *LEPR* gene.

1. Introduction

The World Health Organization has stated that physical inactivity is the 4th leading global risk for mortality in the world which is responsible for raising the risk of chronic diseases, such as diabetes, cardiovascular disease, and several cancers [1]. On the other hand, physical activity (PA) has been shown to be associated with reductions in the risk of all-cause mortality [2] and in the prevalence of cardiovascular disease [3] and stroke [4]. However, despite the well-known health benefits of PA, it is apparent that a large proportion of the general population may not be sufficiently active to derive these benefits. Moreover, the progressive decrease in PA is a serious concern in developed countries [5].

Recent studies have suggested that the amount of PA is influenced by genetic as well as social, environmental, and psychological factors [6–8]. Stubbe et al. reported that the heritability estimate of PA level in 37,051 twin pairs from seven countries was 62% and ranged from 48% to 71% (excluding Norwegian males) [8]. In addition, several

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candidate genes of genetic factors related to PA level have been explored [9–12]. *Leptin* and *leptin receptor* (*LEPR*) genes have been reported as obesity genes that are related to energy homeostasis or food intake [13], and deficiencies of these genes resulted in a decreased locomotor activity in mice. Leptin-deficient *obob* mice show profoundly that a decreased locomotor activity and treatment of *obob* mice with leptin increased locomotor activity and substantially decreased body weight [14,15]. Moreover, LEPR-deficient *dbdb* mice have been shown to be hypoactive, and restoration of LEPR in arcuate neurons of the hypothalamus where leptin receptors are strongly expressed markedly increased locomotor activity in *dbdb* mice [16,17].

The LEPR is a single-transmembrane domain receptor of the cytokine receptor family with a widespread tissue distribution [18,19]. Various genetic variations of the *LEPR* gene have been identified [20,21]. Among them, the Gln223Arg (Q223R) polymorphism (rs1137101), characterized by an adenine (A) to guanine (G) transition at position 668 in exon 6, is one of the most common and results in an amino acid substitution in the extracellular domain. Studies using the meta-analysis of the associations between obesity [22,23] or BMI and waist circumference [24] and Q223R polymorphism of the *LEPR* gene have been conducted, and the RR genotype was reported to be related to obesity stratified by a BMI cutoff value of 25 [22]. With regard to PA level, Q223R polymorphism of the *LEPR* gene was reported to be related to PA energy expenditure in a questionnaire study in prepubertal boys [25] and 24-h energy expenditure in a respiratory chamber [26]. However, Walsh has reported no association between Q223R polymorphism of the *LEPR* gene and PA assessed by the questionnaire [27]. These studies were limited to young people, limited environment or subjective assessment of PA. There have been no studies of the relation between the objectively measured amount of PA and the *LEPR* gene polymorphism in free-living subjects.

We hypothesized that the RR genotype of the Q223R polymorphism in the *LEPR* gene may be associated with shorter time spent in PA than the QQ/QR genotypes. The purpose of this cross-sectional study was to investigate the relation between the objectively measured PA and *LEPR* Q223R polymorphism in free-living Japanese men and women.

2. Methods

2.1. Subjects

The subjects were recruited from people participating in a Nutrition and EXercise Intervention Study (NEXIS, registered at ClinicalTrials.gov, Identifier: NCT00926744). In NEXIS, recruitment was performed throughout the years from 2007 to 2012. A total of 829 people were asked to participate in this study, and 822 accepted. Subjects with a history of stroke, cardiac disease, chronic renal failure, or difficulty with ambulation due to knee or back pain were excluded from the study because their PA could be partly influenced by their disease or pain. Finally, the baseline data of 556 Japanese adults (149 men and 407 women), 24–65 years of age, were analyzed in this cross-sectional study. All subjects gave written informed consent for participation in the present study. All procedures were reviewed and approved by the Ethics Review Board of the National Institute of Health and Nutrition.

A total of 556 Japanese adults (149 men and 407 women), 24–65 years of age, participated in this cross-sectional study. Subjects with a history of stroke, cardiac disease, chronic renal failure, or difficulty with ambulation due to knee or back pain were excluded from the study because their PA could be partly influenced by their disease or pain. All subjects gave written informed consent for participation in the present study. All procedures were reviewed and approved by the Ethics Review Board of the National Institute of Health and Nutrition.

2.2. Anthropometry and biochemical measures

Weight and height were measured and body mass index (in kg/m^2) was calculated. We assessed several risk factors to investigate the relations between risk factors and *LEPR* gene polymorphisms. Percent body fat was determined by dual-energy X-ray absorptiometry (Hologic QDR-4500; Hologic, Waltham, MA) with subjects in the supine position. Waist circumference was measured around the abdomen at the level of the navel at the late expiratory phase using a tape measure. Blood pressure was measured with form ABI/PWV (Omron Corlin, Tokyo, Japan) under quiet resting conditions in the supine position. Venous blood withdrawn from the antecubital vein was collected into tubes without additives or with EDTA, and immediately centrifuged at 3000 rpm for 20 min to obtain serum or plasma, respectively. Glucose and HbA1c in plasma and HDL-cholesterol (HDL-C) and triglyceride (TG) in serum were determined. All measurements were performed after an overnight fast of at least 10 h.

2.3. Evaluation of physical activity

The duration and intensity of PA were evaluated by triaxial accelerometry (Actimarker EW4800; Panasonic Electric Works, Osaka, Japan), which has been shown to be a valid method for determining the total energy expenditure or energy expenditure associated with PA based on a comparison with double-labeled water [28]. The subjects were asked to wear the accelerometer on the lower back except during water-based activities for 4 weeks. The metabolic equivalent (MET) intensity levels of PA were calculated as described previously [28,29]. Briefly, acceleration in the anterior–posterior (x), mediolateral (y), and vertical (z) axes was calculated using a sensor with a sample rate of 20 Hz over a range from 0 to $2 \times g$. The apparatus stored the standard deviation of the vector norm of the composite acceleration (K_m) in three dimensions each minute. The metabolic equivalent (MET) intensity levels of PA were calculated by simple linear regression of *K*m. The average total energy expenditure (kcal/day), daily step counts (steps/day), and the total amount of PA over 3 METs (moderate to vigorous PA: MVPA) (METs·h/week) were calculated using data from at least 2 weeks excluding those days where subjects did not wear the accelerometer. We also calculated the daily time spent in PA of each intensity (min/day) to evaluate which PA intensity was especially related to the *LEPR* genotype. We calculated the time spent corresponding to 1.1–2.9 METs (light), 3.0–5.9 METs (moderate), and more than 6.0 METs (vigorous) [30], and calculated the time of less than 1.1 MET by subtracting the sum of times of light, moderate, and vigorous PA from 1440 min (inactive time).

2.4. Genotyping of the LEPR gene

Genomic DNA was extracted from the plasma buffy coats using a QIAamp DNA Blood Maxi Kit (Qiagen, Tokyo, Japan). The *LEPR* Q223R genotype was determined by real-time PCR with TaqMan probes using an ABI Prism 7700 Sequence Detector (Applied Biosystems, Foster City, CA). In a preliminary study, we examined the precision of genotyping by the TaqMan method, and the concordance rate between two samples obtained on different days from 290 subjects was 100% (data not shown). The gene-specific primers and TaqMan probes for SNP were synthesized using Primer Express v.1.5 software (Applied Biosystems) according to the published DNA sequences for SNPs as follows: Q223R in exon 6 of the *LEPR* gene (NCBI dbSNP #rs1137101). The sequences of the oligonucleotides used were as follows:

LEPR forward: 5′-TGTTTGAAAATCACATCTGGTGGAGTA-3′
LEPR reverse: 5′-CCCATATTTATGGGCTGAACTGACA-3′
LEPR/Q probe: 5′-TTAGAGGTGACTGGAAAA-3′
LEPR/R probe: 5′-AGGTGACCGGAAAA-3′.

PCR was performed according to the manufacturer's directions. Ninety-six-well PCR plates were read on an ABI-7700 with end-point analysis mode of the SDS v.1.7a software package (Applied Biosystems). Genotypes were determined automatically by the signal processing algorithms in the software.

2.5. Statistical analyses

Data were expressed as means ± standard deviation. The *t* test was used to compare the variables between men and women or genotype groups, and one-way ANOVA was used to compare the variables among genotype groups followed by the Scheffé's test for multiple comparisons. The chi-squared test was used to determine the frequency of distribution or to assess the Hardy–Weinberg equilibrium. Pearson's correlation coefficients (r) were calculated to evaluate the associations between PA level and age. ANCOVA adjusted for age and sex was used to test the association between PA and *LEPR* genotype. Genotype was first assessed in three genotype categories (QQ, QR, and RR genotypes), which is an additive model of inheritance, and then grouped into two categories, QQ/QR and RR, which is the Q dominant model of inheritance. We did not perform analysis by the Q recessive model because the sample size of the QQ genotype was too small.

Statistical significance was set at $P < 0.05$. All statistical analyses were performed with SPSS for Windows, version 20.0 (SPSS Japan Inc., Tokyo, Japan).

3. Results

The physical characteristics and PA variables in this study are shown in Table 1. Women were significantly older, and had lower BMI, fasting blood glucose, TG, and blood pressure than men ($P < 0.05$). There were no difference in the amount of MVPA and step counts per day between men and women. In contrast, men had longer times spent in vigorous PA and inactivity than women, whereas shorter times spent in light PA ($P < 0.05$). The amounts of MVPA and step counts were negatively associated with age in both men and women ($r = -0.21$ and $r = -0.17$, respectively, $P < 0.05$).

The distribution of Q223R polymorphism was QQ 0.7%, QR 22.6%, and RR 76.6%. This genotype distribution was similar to those reported previously for other Japanese populations [31]. Allelic distribution was consistent with the Hardy–Weinberg equilibrium ($P > 0.05$). There were no significant differences in season in which the experiment was performed that may have affected the levels of physical activity among genotypes.

Table 2
Associations of LEPR genotype with physical and metabolic characteristics.

	LEPR genotype (additive model)		
	QQ (n = 5)	QR (n = 122)	RR (n = 429)
Age (years)	47.8 ± 8.0	49.3 ± 10.9	50.5 ± 9.7
Sex (men/women, %men)	2/3, 40%	26/96, 21%	121/308, 28%
Height (cm)	161.8 ± 6.7	160.3 ± 7.6	160.6 ± 8.5
Weight (kg)	59.9 ± 6.5	58.2 ± 11.0	58.9 ± 11.8
Body mass index (kg/m^2)	22.9 ± 2.3	22.6 ± 3.3	22.7 ± 3.5
%Fat (%)	23.6 ± 8.1	26.9 ± 6.3	26.3 ± 6.6
Fasting plasma glucose (mg/dL)	91.4 ± 10.1	89.8 ± 10.5	90.6 ± 13.5
HbA1c	5.3 ± 0.5	5.4 ± 0.4	5.4 ± 0.6
Triglycerides (mg/dL)	69.0 ± 31.0	84.2 ± 53.2	92.2 ± 58.2
HDL-cholesterol (mg/dL)	72.6 ± 20.4	66.1 ± 14.3	64.4 ± 16.3
Systolic blood pressure (mm Hg)	127.6 ± 16.9	117.2 ± 13.9	117.7 ± 15.1
Diastolic blood pressure (mm Hg)	83.7 ± 11.9	70.3 ± 10.1 *	71.5 ± 10.8 *

Values are presented as means ± standard deviation.
* $P < 0.05$ vs QQ genotype by ANOVA.

There were no differences in age, sex distribution, height, weight, BMI, percentage body fat, or risk factors except diastolic blood pressure among genotypes ($P < 0.05$, Table 2). On the other hand, the prevalence of dyslipidemia, which was defined as triglyceride ≥150 mg/dL or 40 mg/dL <HDL-C according to the Japanese guidelines, was higher in the RR genotype ($P < 0.05$).

The relation between the *LEPR* genotype and the amount of PA was analyzed by ANCOVA with age and sex as covariates in the additive model. There were no significant associations between genotypes and each PA variable (Table 3). Next, we performed analysis in the Q dominant model. There were significant associations between the *LEPR* genotype and the time spent in light PA or inactive time. The time spent in light PA in the RR genotype was significantly shorter than that in the QQ/QR genotype ($P < 0.05$, Fig. 1). The inverse association was observed between the time spent in inactivity and the Q223R polymorphism. There were no such differences in the time spent in moderate or vigorous PA. The analysis was performed in each sex separately, and significant associations were found only in women. In women, the time spent in light PA in the RR genotype was significantly shorter than that in the QQ/QR genotype (RR: 584.2 ± 100.2 vs QQ/QR: 608.1 ± 100.2 min/day, $P < 0.05$), and the time spent in inactive time in the RR genotype was significantly longer than that in the QQ/QR genotype (RR: 790.0 ± 105.5 vs QQ/QR: 763.9 ± 105.5 min/day, $P < 0.05$).

Table 1
Subjects characteristics in the present study.

	Men (n = 449)	Women (n = 407)	*P* value
Age (years)	47.0 ± 10.5	51.4 ± 9.6	$P < 0.05$
Height (cm)	170.2 ± 6.3	157.0 ± 5.7	$P < 0.05$
Weight (kg)	69.8 ± 12.1	54.7 ± 8.3	$P < 0.05$
Body mass index (kg/m^2)	24.0 ± 3.5	22.2 ± 3.3	$P < 0.05$
%Fat (%)	20.7 ± 4.6	28.6 ± 5.9	$P < 0.05$
Fasting blood glucose (mg/dL)	92.9 ± 12.9	89.5 ± 12.7	$P < 0.05$
HbA1c	5.4 ± 0.6	5.4 ± 0.5	
Triglycerides (mg/dL)	119.9 ± 72.0	79.4 ± 46.0	$P < 0.05$
HDL-cholesterol (mg/dL)	54.2 ± 11.8	68.8 ± 15.4	$P < 0.05$
Systolic blood pressure (mm Hg)	121.6 ± 13.1	116.3 ± 15.3	$P < 0.05$
Diastolic blood pressure (mm Hg)	76.5 ± 10.5	69.5 ± 10.2	$P < 0.05$
Total energy expenditure (kcal/day)	2279.0 ± 280.2	1870.3 ± 189.8	$P < 0.05$
Daily steps (step count/day)	10873.6 ± 3044.5	10737.6 ± 3567.5	
The amount of moderate to vigorous PA (METs·h/week)	29.9 ± 15.4	29.1 ± 15.4	
Time spent of light PA (min/day)	493.2 ± 109.9	590.0 ± 102.0	$P < 0.05$
Time spent of moderate PA (min/day)	60.0 ± 22.8	64.5 ± 25.3	
Time spent of vigorous PA (min/day)	3.9 ± 8.5	1.8 ± 7.0	$P < 0.05$
Inactive time (min/day)	882.8 ± 112.3	783.6 ± 107.2	$P < 0.05$

Values are presented as means ± standard deviation.
PA; physical activity.

Table 3
Associations of LEPR genotype with physical activity level.

	LEPR genotype (additive model)		
	QQ (n = 5)	QR (n = 122)	RR (n = 429)
Total energy expenditure (kcal/day)	2069.9 ± 209.3	2000.7 ± 209.9	1972.8 ± 209.2
Step counts (steps/day)	12927.2 ± 3435.9	11050.1 ± 3445.5	10670.5 ± 3437.1
The amount of moderate to vigorous PA (METs·h/week)	43.2 ± 15.3	29.8 ± 15.3	29.0 ± 15.3
Time spent of light PA (min/day)	593.3 ± 102.9	579.4 ± 103.2	559.4 ± 103.0
Time spent of moderate PA (min/day)	85.8 ± 24.7	64.3 ± 24.7	62.8 ± 24.7
Time spent of vigorous PA (min/day)	6.0 ± 7.3	2.4 ± 7.4	2.4 ± 7.3
Inactive time (min/day)	754.9 ± 107.5	793.9 ± 107.8	815.5 ± 107.5

Values are presented as means ± standard deviation by ANCOVA adjusted for age and sex.
PA; physical activity.

4. Discussion

We examined whether the Q223R polymorphism of the *LEPR* gene was associated with individual differences in the amount or time spent in PA in healthy Japanese adults. The RR genotype was associated with shorter time spent in light PA and longer time spent in inactivity. Light PA is characterized by non-exercise activity thermogenesis (NEAT), such as domestic work or standing, and also spontaneous PA that is unconscious, non-volitional movement [32]. Thus, the *LEPR* may be involved in the regulation of NEAT or spontaneous PA as typified by light PA. These results represent the first evidence of an association between *LEPR* genotype and type of objectively assessed PA.

In a previous study, Q223R polymorphism of the *LEPR* gene was reported to be related to PA energy expenditure based on 24-h energy expenditure in a respiratory chamber. The RR genotype was associated with lower PA level compared to the QQ genotype [26], which was consistent with the present results. Richert et al. also reported that the RR genotype was associated with lower PA energy expenditure in prepubertal boys assessed by means of a questionnaire based on self-reported time spent on sports, recreational activity, and usual walking and cycling [25]. The intensity of PA they assessed was moderate-to-vigorous PA, while a significant difference was observed in light PA in the present study. This discrepancy of intensity of PA may have been due to the different assessment methods used, different generation [33], or country [34]. On the other hand, Walsh et al. reported no association between the Q223R polymorphism of the *LEPR* gene and PA in adults [27]. They used a self-reported PA questionnaire, while Stefan et al. [26] and present study that were investigated in adults assessed PA using objective methods that could include unconscious physical activity. These methodological differences may bring different findings. Moreover our results suggested that there was a gender difference in the associations between polymorphisms of the *LEPR* gene and PA. A previous study regarding the effects of *LEPR* Q223R genotype on blood leptin level showed that the RR genotype was associated with higher leptin levels only in women [35]. However the sample size of men in the present study was smaller than that of women. Further studies are

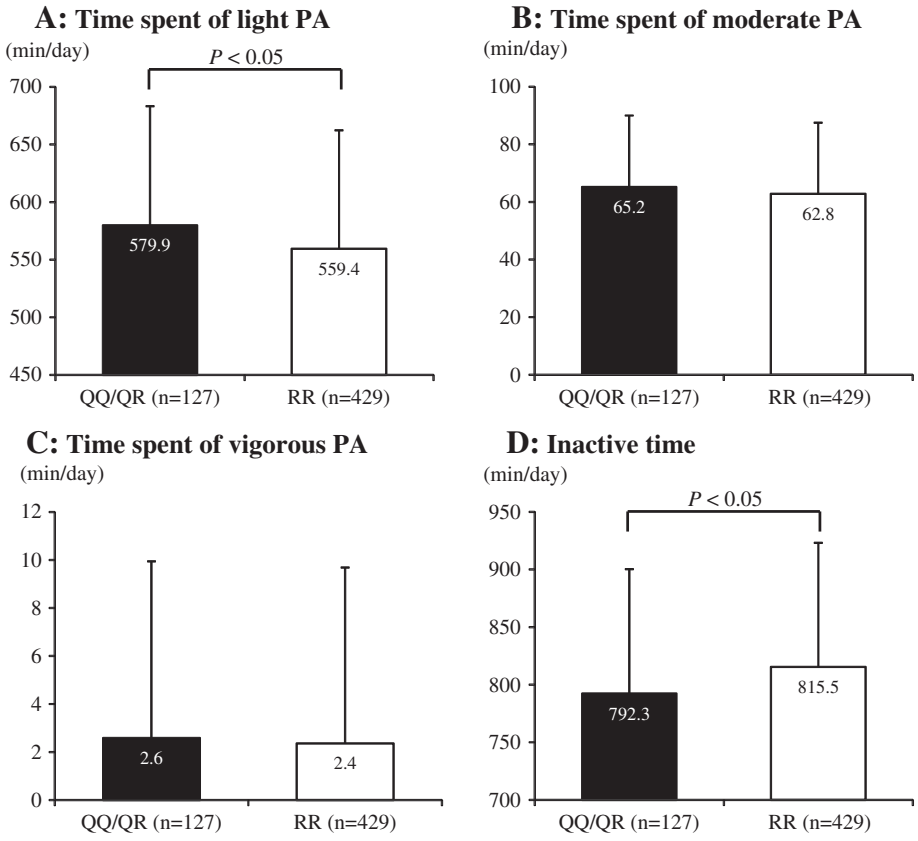

Fig. 1. Differences in time spent in physical activity of each intensity between the QQ/QR genotype and RR genotype. A: light PA (1.1–2.9 METs), B: moderate PA (3.0–5.9 METs), C: vigorous PA (≥6.0 METs), D: inactive time (1440 min—sum of times of light, moderate, and vigorous PA). Values are presented as means by ANCOVA adjusted for age and sex.

needed to investigate the associations between polymorphisms of the *LEPR* gene and PA in a larger sample of men.

Leptin and leptin receptor play pivotal roles in the regulation of energy homeostasis via energy expenditure and food intake. Leptin-deficient *obob* mice have profoundly decreased locomotor activity [14,15]. Treatment of *obob* mice for three weeks with pharmacological doses of leptin increased locomotor activity and substantially decreased adiposity [15]. In addition, leptin receptor-deficient *dbdb* mice show hypoactivity, and restoration of leptin receptors in arcuate neurons greatly increases locomotor activity in these mice [17]. Furthermore, the R allele has been shown to have lower serum leptin-binding activity that may reflect receptor function than the Q allele [36]. Therefore, the *LEPR* genotype likely influences human PA level via leptin binding activity in the hypothalamus. Our data suggest that *LEPR* gene may be involved in induction of spontaneous PA as NEAT rather than conscious PA with moderate-to-vigorous PA in humans. Although *LEPR* gene seems to be associated with spontaneous PA in humans, the detailed mechanisms remain unclear, and additional functional studies are required.

The difference of 20 min in light PA between genotype groups in the present study was 20 kcal/day, given light PA = 2.0 METs and weight = 60 kg (QQ/QR genotype; 2.0 METs × 60 kg × 1/3 h = 40 kcal, RR genotype; 1.0 METs × 60 kg × 1/3 h = 20 kcal). This calculation was performed following Ainsworth et al. [32] who recommended that 3.5 mL/kg/min (=1 MET) is equal to 1.0 kcal × kg/h. Furthermore, this difference in energy expenditure will cause about 1 kg difference in weight per year if 7000 kcal energy expenditure is comparable to 1 kg of weight loss [37], Moreover, the RR genotype of Q223R polymorphism has been reported to be related to prevalence of obesity (22, 23). Therefore, shorter time spent in light PA in the RR genotype may reduce the risks of obesity or chronic diseases.

In the present study, we did not examine the effects of other genetic, social, or environmental factors on PA level. Individual differences in PA level in humans are very complex and seem to be influenced by multiple genetic and environmental factors. In the future, it will be necessary to study the effects of multiple genetic factors and interactions with environmental factors on PA level simultaneously. In addition, we did not perform analysis by the Q recessive model because the sample size of the QQ genotype was too small. However, the QQ genotype showed a higher PA level, although this was not significant. Further studies are required in a larger population.

In conclusion, the RR genotype of Q223R polymorphism in the *LEPR* gene was associated with shorter time spent in light PA and longer inactive time. It has been suggested that the variety of PA level in humans is partly caused by the diversity of the *LEPR* gene. In addition, LEPR may be associated with induction of spontaneous PA as non-exercise activity thermogenesis rather than conscious PA with moderate-to-vigorous PA in humans.

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Disclosures

The authors declare that they have no conflicts of interest.

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