Genomic predictors of fat mass response to the standardized exercise training

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ABSTRACT

To explore the genetic architecture underlying exercise-induced fat mass change, we performed a genome-wide association study with a Chinese cohort consisting of 442 physically inactive healthy adults in response to a 12-week exercise training (High-intensity Interval Training or Resistance Training). The inter-individual response showed an exercise-induced fat mass change and ten novel lead SNPs were associated with the response on the level of $P<1\times10^{-5}$. Four of them (rs7187742, rs1467243, rs28629770 and rs10848501) showed a consistent effect direction in the European ancestry. The Polygenic Predictor Score (PPS) derived from ten lead SNPs, sex, baseline body mass and exercise protocols explained 40.3% of the variance in fat mass response, meanwhile importantly the PPS had the greatest contribution. Of note, the subjects whose PPS was lower than -9.301 had the highest response in exercise-induced fat loss. Finally, we highlight a series of pathways and biological processes regarding the fat mass response to exercise, e.g. Apelin signaling pathway, insulin secretion pathway and fat cell differentiation biological process.

Keywords: Genome Wide Association Study; High-intensity interval training; Resistance training; Polygenic Predictor Score; Inter-individual Variability

Introduction

Physical inactivity is a risk factor for non-communicable diseases [1]. The global data across 168 countries shows that 7.2% and 7.6% of all-cause and cardiovascular disease deaths were attributable to physical inactivity [2]. Nevertheless, the global prevalence of insufficient physical activity was 27.5% [3], and the standardized prevalence of physical inactivity increased from 22.12% to 28.79% during 2013-2019 in China [4]. Physical inactivity indicates higher adiposity, while the active individual has a lower body fat percentage under the same body mass index (BMI) [5]. The Mendelian randomization study [6] revealed that higher BMI and particularly fat mass index are associated with increased risk of aortic valve stenosis and several cardiovascular conditions including aortic valve stenosis, heart failure, deep vein thrombosis, peripheral artery disease, coronary artery disease and others.

Exercise is the most effective way to avoid physical inactivity. The World Health Organization (WHO) in 2020 recommended at least 150-300 min of moderate-intensity or 75-150 min of vigorous-intensity physical activity per week [7]. High-intensity interval training (HIIT) shows significant benefits to improve body composition and cardiorespiratory fitness (CRF) [8], and is especially more effective than moderate-intensity continuous training (MICT) in reducing abdominal/visceral fat mass [9]. Resistance training (RT) is effective in changing body composition by significantly decreasing fat mass, and increases in appendicular lean mass relative to fat mass when compared to aerobic training alone or the combined intervention [10]. Meanwhile, the inter-individual variability that occurs in fat mass loss in response to exercise training is not different between HIIT and MICT [11]. The total and abdominal adipose tissue changes following the exercise training also show the inter-individual differences [12].

The heritability estimates for body fat mass are greater than 70% [13]. The genetic architecture underlying the exercise-induced VO_2max response [14], muscle fiber hypertrophy response [15], muscle strength response [16] have all been examined. Nevertheless, the genomic predictors of fat mass response to exercise are currently not well understood. The only research on the Genome Wide Association Study (GWAS) of exercise-induced fat loss showed that the Single Nucleotide Polymorphism (SNP) rs116143768 T allele in the ACSL1 (*Acyl-CoA synthetase long chain family member 1*) gene was associated with higher aerobic training induced fat loss efficiency ($P< 5 \times 10^{-8}$) in 126 Polish women [17]. However, the explanation of a single SNP is limited, since the polygenic effect wasn't described either. It is not known whether other variants would modify the fat mass response to the exercise training and need more examination or the studies based on the genome level.

Overall, the aims of this study were to examine the inter-individual fat mass response to standardized

exercise training and to explore the top variants related to the exercise-induced fat mass change utilizing a genome-wide association study (GWAS). The objectives also include exploring the explanation of Polygenic Predictor Score (PPS) and phenotype in the inter-individual variability of fat mass response, and describe the potential mechanism to the individual differences in the fat mass response to exercise.

Materials and Methods

Experimental approach to the problem

We utilized data from the 12-week exercise training in a Chinese population from 2019.07 to 2021.01 [18] in the discovery stage. We employed a GWAS approach to examine the fat mass response to 12-week exercise training in the Chinese cohort. The DNA findings of Chinese cohort were validated in European ancestry [17]. Then, the polygenic predictor score (PPS) was calculated to construct the predicting models of fat mass response to exercise, and gene mapping and function analysis was performed to explore the potential biological mechanisms. The study protocol was approved by the Sports Science Experimental Ethics Committee of an institution affiliated with one of the authors (NO. 2019191H) and the subjects were informed of the benefits and risks of the exercise training prior to signing a Sports Science Experimental Ethics Committee approved informed consent document to participate in the study. The study design is shown in Figure 1.

****** Figure 1. Study design ******

Subjects

Physically inactive Chinese were recruited based on the Global Physical Activity Questionnaire (GPAQ)[19, 20]. The subjects who took medication or other supplements and had injuries or cardiovascular or metabolic diseases within last six months were excluded. The GPAQ and the Food Frequency Questionnaire (FFQ) including 100 items[21, 22] were used to assess the daily physical activity and dietary intake. All subjects were required to keep their daily activities and dietary intake consistent through the 12-week exercise.

A total of 345 participants were recruited for the HIIT group and 220 participants for the RT group.Out of these, 330 participants in the HIIT group and 206 in the RT group completed the 12-week exercise interventions with 100% attendance. We excluded those subjects whose genotype experiments were not performed (N=63), who failed in the genome sample quality control (N=24), or whose fat mass change values were missing or were three Standard Deviation (SD) from the average value (N=7). A total of 442 Chinese participants, including 263 in HIIT group and 179 in the RT group, were analyzed as the Chinese cohort. The Chinese cohort consisted of 210 males (Height: 175.4±6.2 cm, BM: 70.9±14.0 kg, BMI: 23.0±4.0) and 232 females (Height: 162.2±6.1cm, BM: 55.1±9.1kg, BMI: 20.9±3.0) who were physically inactive adults (ages: 20±2 years).

Exercise programs

Two exercise modalities (HIIT and RT) were employed in this study. Meanwhile, the training protocols were designed according to the guidelines provided by the American College of Sports Medicine (ACSM) [23, 24] and all training sessions were conducted under supervision.

The HIIT program consisted of a total of 36 sessions with running at 80-90% VO_2max and recovery intervals at 50-55% VO_2max in the field. The progressive HIIT was conducted (3 sessions per week and ≥1 day between consecutive training days). The training started with a total of 56 bouts of 15 s running interval 15 s recovery in the first week, followed with 28 bouts of 30 s running interval with 30 s recovery were executed in the second week. In the third week, 14 bouts of 1 min running interval with 1 min recovery in the third week, followed by 7 bouts of 2 min running interval with 2 min recovery. Then, a total of 4 bouts of 4 min running interval with 3 min recovery was conducted in the following 8 weeks. Each session began with a 10 min warm up and ended with 3 min of active recovery. The individuals' intensities were

determined by the individual VO_2max, and the Polar belts (Polar H10, Polar, Finland) were utilized to monitor the target Heart Rate (HR). Each subject performed the maximal exercise tests to measure individual VO_2max on a cycle ergometer (Monark, 839E) with a metabolic measurement cart (Cortex, MetaMax 3B). The measurement of VO_2max was conducted as described previously [18].

The RT program consisted of a total of 24 sessions with the 70% one-rep max (1RM) (2 sessions per week and ≥2 days between consecutive training days). Subjects performed 5 sets each of both the bench press and back squat at a 70% of their 1RM load, with 2 min rest period of between sets. A 10 min warm-up and 10 min of stretching were performed before and after each training session. The individual's workloads were adjusted by the measurement of 1RM every four weeks. The 1RM test commenced with back squats/ bench presses at 40% of an individual's estimated 1RM for warm-up. Subjects performed 3-5 repetitions at the weight of increment of 15-20kg than warm-up weight. After 2-4 min rest, subjects completed 2-3 back repetitions with increasing weight by 15-20 kg (for back squats) or 5-10 kg (for bench presses). Then the process was repeated following a rest of 2-4 min until they reached their maximal effort. A decreasing load (5-10 kg for back squats, or 2.5-5kg for bench presses) was performed after 2-4 min rest. The weight was increased or decreased until they completed the 1RM lifting by the standard technique. The 1RM weight was determined within five attempts.

Body composition measurement

Body composition was measured in the morning after a night of fasting prior to and after the 12-week exercise training. The Body Mass (BM) and body fat mass (BFM) were measured by Bioelectrical Impedance Analysis (BIA) with 8-point Tactile Electrode method (Inbody230, Biospace, South Korea).

Genotyping and imputation

Genomic DNA was extracted from venous blood leukocyte samples and the genotyping was performed with Illumina Chinese Genotyping Array (CGA, Illumina, USA). For sample quality control (QC), we excluded individuals with a sample call rate <0.95, outliers from the extreme heterozygosity (3SD) and principal component analysis(3SD). For QC of SNPs, the variants with missing genotype rate>3%, a low minor allele frequency (MAF) < 0.01, and the Hardy-Weinberg exact test with a threshold of P value $<1\times10^{-6}$ were removed by Plink (v1.9).

Genotype harmonizer 1.4.20 was used to align strands. Pre-phasing the autosome data by SHAPEIT2 and imputation by IMPUTE 2 with the reference panel of Chinese Han Beijing (CHB) samples from 1000 Genome Projects Phase 3 (1KGP) Build 37. After imputation, we retained variants with INFO ≥0.8 and MAF ≥0.03 for association and downstream analysis.

Statistical Analyses

Fat mass response

We evaluated the individual's fat mass response by BFM change, which was calculated by the equation: $\text{BFM change} = 100\% \times \frac{\text{post BFM}-\text{baseline BFM}}{baseline\ BFM}$. The participants were separated by the quartiles of BFM change. The normality BFM change was assessed by the Shapiro-Wilk test. The participants were separated by the quartile of BFM change. The baseline BFM and post BFM was compared by Paired Samples Test (IBM SPSS Statistics 29.0). The BFM change between the genotype of each lead SNP was compared using a One-way ANOVA.

Genome-wide association study

The sex, age, height, baseline BM, exercise protocols and the top 5 principal components (PCs) were included as covariates in the linear regression analysis performed by PLINK1.9 for the Chinese cohort. The

suggestive significance level of $P<1\times10^{-5}$ was set to select the genome-wide significance variants. The GWAS threshold of $P<1\times10^{-4}$ were validated in the Polish cohort. Genomic inflation factor λ and quantile-quantile (Q-Q) plot were generated to compare the distribution of our data with the expected distribution (R version 4.1.2). Lead SNPs analysis and gene mapping were performed in Functional Mapping and Annotation platform (FUMA) [25]. The Manhattan Plot was generated to show the GWAS result (R version 4.1.2). Lead SNPs were separately involved into the liner regression model which comprised of top 5PCs. The partial R^2 for each lead SNP was calculated as the proportion of variance in phenotype explained (PVE).

The external validation in individuals of European ancestry

The DNA findings from the Chinese cohort were validated in European ancestry cohort [17]. The lead SNPs and those reaching a significance level of 1×10^{-4} in the Chinese cohort were validated in the Polish cohort, and the SNPs those reaching a level of $P<0.05$ in the Polish cohort and had the same effect allele in both the Chinese cohort and the Polish cohort were defined as the replicated variants. A meta-analysis of the replicated variants in the Chinese and Polish cohort was performed using the Metal tool(http://www.sph.umich.edu/csg/abecasis/Metal/).

Polygenic Predictor Score and Fat mass response

The lead SNPs weighted by beta coefficient in GWAS results were used to calculate the polygenic predictor score (PPS) for individuals by the following equation [14]:

$$\mathrm{PPS} = \beta_1 \times n_1 + \beta_2 \times n_2 \cdots \beta_i \times n_i$$

In the equation, n is the number of effect allele in each selected SNPs, i is the number of selected SNPs, β is the beta coefficient in GWAS results.[3] The comparison between the PPS of each quartile was examined by One-Way ANOVA (IBM SPSS

Statistics 23). The phenotypes (sex, age, height, baseline BM and baseline BFM), the PPS, the top 5 PCs and the exercise protocols were added as the predictors. The association between the predictors and the BFM change was analyzed in the method of liner stepwise regression (IBM SPSS Statistics 23). The entry criterion was the probability of $F < 0.05$ and the removal criterion was > 0.10. The variance inflation factor (VIF) < 10 and tolerance ≤ 1 was accessed to avoid multiple collinearities. Significance was set at $P < 0.05$.

Gene function analysis

Genes were defined as all transcripts from Ensembl gene build 85 including non-protein coding genes and RNAs. The mapping genes were performed to KEGG pathway and GO biological processes analysis by Metascape tools[26] (https://metascape.org).

Results

The BFM decreased 2.37±12.22% on average after 12 weeks of exercise training (P<0.001, 95%CI: -0.69~ -0.32). Subjects who conducted the HIIT program had a greater number of fat loss responders (the 1st Quartile and the 2nd Quartile) than who performed the RT program (Table 1). There was variability in the individual BFM change after 12 weeks of exercise training, and some individuals didn't show an improvement in fat mass (Figure 2).

****** Table 1. The BFM change after 12-week exercise training. ******

****** Figure 2. The distribution of BFM changes following 12 weeks of exercise. ******

The Q-Q plot and genomic inflation factor of 1.006 show no evidence of inflation in the study (Supplemental Figure S1). None of variants reached the typical threshold for genome-wide significance ($P<5\times10^{-8}$, Figure 3.). Ten lead SNPs were associated with fat mass response to exercise with the threshold of $P<1\times10^{-5}$ (Table 2).

****** Figure 3. The Manhattan plot of fat mass response to exercise GWAS results ******

****** Table 2. The lead SNPs of fat mass response to exercise GWAS. ******

The most significant association was found for rs7187742 on a long intervening/intergenic non-coding RNA (lincRNA) gene RP11-354I13.2 (P=1.50×10^{-7}, PVE=3.6%). The CC carriers (N=322) had a 4.0% and 11.7% lower in average BFM change after exercise than TC carriers (N=111) and TT carriers (N=9) (P<0.05, 95%CI: -3.52~-1.23. Figure 4a). The homozygote GG (N=7) of SNP rs1467243 (P=7.98×10^{-7}, PVE=5.7%), which is on the intron of FRRS1L (*Ferric chelate reductase 1 Like*) gene, had an 8.9% and 14.6% lower in average BFM change than heterozygote GC (N=106) and homozygote CC (N=325) (P<0.05, 95%CI: -3.47~-1.17. Figure 4b). The C allele of the SNP rs10848501 was highly associated with the more effective fat loss (P= 6.27×10^{-6}). The homozygous CC (N=83) has about 4% lower in average BFM change than heterozygote CT (N=201) and 8% greater BFM decrease than homozygous TT (N=128) after 12-week exercise training (P<0.05, 95%CI: -3.84~-1.44. Figure 4c).

****** Figure 4. The BFM change after exercise in different genotype of the top SNPs. ******

The external validation was conducted in the Polish cohort [17]. None of genome-wide suggestive significance variants (P<1×10^{-5}) in the Chinese cohort reached the significance level (P<0.05) in the Polish cohort. Whereas, four lead SNPs (rs7187742, rs1467243, rs28629770, rs10848501) showed the same directions in the Poland cohort (Table 3). Furthermore, a total of 39 SNPs with the level of P<1×10^{-4} were replicated in the Polish cohort (P<0.05, Supplemental table S1). Significantly, there were 33 SNPs (Position: 103983271-104051855) in the Chromosome 2. The SNP rs450092 in ZNF385D *(Zinc finger protein 385D)* gene, the SNP rs17086640 and rs4554332 in intergenic of Chromosome 6, as well as the SNPs (SNP rs4634608, rs5004001 and rs28672867) in the CIBAR1-DT *(CIBAR1 divergent transcript)* gene in Chromosome 8 were replicated in the Polish cohort (P<0.05). The SNP rs72833512 in intergenic of Chromosome 2 was the top variant (P=1.77×10^{-7}) in meta-analysis (Supplemental table S1).

****** Table 3. The validation of top SNPs in Polish cohort ******

The significant SNPs were mapped on 48 genes, and they involved in the KEGG pathways as the insulin secretion, GnRH signalling pathway, Glucagon signalling pathway, Estrogen signalling pathway, Apeling signalling pathway, cGMP-PKG signalling pathway, Wnt signalling pathway, Lipid and atherosclerosis and Calcium signalling pathway (Figure 5a). They also showed the influence in fat cell differentiation biological process (GO:0045444; $P = 4.14 \times 10^{-5}$, Figure 5b).

****** Figure 5. The KEGG pathway and GO analysis results with the mapping genes. ******

When the subjects were separated by the quartile of BFM change, the PPS showed significant differences between the sub-groups ($F=41.418$, $p<0.05$, Figure 6). The post hoc test Bonferroni correction showed that the PPS of the subjects in the 1st Quartile had the lowest PPS ($p<0.05$), and the subjects in the 4th Quartile had the highest PPS ($p<0.05$). Whereas, the PPS between the middle two Quartiles showed no significant differences ($p>0.05$). The subjects whose PPS was lower than -9.301(95% CI: -10.970~-7.630) had the highest response in exercise-induced fat loss.

****** Figure 6. The PPS between the subjects in different quartile of BFM change *****

The PPS, baseline BM, exercise protocols and sex could explain 40.3% variance of fat mass response (Table 4). The PPS was the primary factor which influenced the fat mass response (Partial $R^2=0.281$, $p<0.05$).

****** Table 4. The linear regression of the fat mass response to exercise ******

Discussion

To the best of our knowledge, this is the most extensive study examining fat mass response to the standardized exercise training through the GWAS approach, and it represents the first of its kind in the Chinese population. The inter-individual differences in the fat mass response to exercise occurred in both HIIT and RT. Ten lead SNPs were associated with fat mass response on the level of $P<1\times10^{-5}$, and four of them were replicated with the same direction in the independent cohort. The PPS, sex, baseline BM, and

exercise protocols could explain 40.3% of the variance in fat mass response, and the PPS emerged as the primary factor. The subjects whose PPS was lower than -9.301 had the highest response in exercise-induced fat loss. In our study, the BFM change showed inter-individual differences after 12-week exercise training, and the patterns of the individual differences were coincident in HIIT and RT. This finding is in accordant with the fat mass response to 1-year exercise intervention which reported that only 10 of 19 participants were high responders in the HIIT intervention, and 26% of participants increased their total fat mass after the 1-year exercise [11]. The inter-individual differences in fat mass showed different exercise type [11], exercise amount and intensity [12]. Although increasing the exercise intensity and amount [12] contributed to decrease the proportion of non-responders, the inter-individual variability was constant. In our study, the standard supervised exercise training was performed with 100% attendance, and participants maintained consistent daily activities and dietary intake through the 12-week program. The 12-week exercise training improved the subjects' body composition, but not all participants decreased their body fat mass. The variability maybe derived from hereditary factors which have previously been mentioned in the exercise response of VO_2max [14], submaximal exercise heart rate [27], and muscle fiber hypertrophy [15].

According to our findings, ten lead variants were associated with fat mass response on the level of $P<1\times10^{-5}$. The previous study on the Genome Wide Association Study (GWAS) of exercise-induced fat loss showed that the Single Nucleotide Polymorphism (SNP) rs116143768 T allele in the ACSL1 (*Acyl-CoA synthetase long chain family member 1*) gene was associated with higher aerobic training induced fat loss efficiency ($P< 5 \times 10^{-8}$) in 126 Polish women [17], whereas the SNP rs116143768 was not significant in our study. It may derive from the different geographic ancestry or/and the sex difference in the subjects. We found that the top lead SNP rs7187742 ($P=1.50\times10^{-7}$) located in the non-coding RNA gene *RP11-354I13.2* was highly associated with the BFM change, and homozygote TT indicated the worst response in exercise-induced fat

loss. Similarly, the T allele indicated the worse fat loss efficiency in the Polish cohort [17] although it did not reach a level of significant. The association of SNP rs7187742 and obesity trait was showed in FinnGen_R6 on the Open Targets Genetics [28, 29], but the SNP rs7187742 has not been previously reported.

The second lead SNP rs1467243 ($P = 7.98\times10^{-7}$) located in the FRRS1L explains 5.7% variance of the fat mass response to exercise based on our results. The G allele carriers showed a more efficient fat loss after 12-week exercise training. Interestingly, none of the non-response subjects (BFM change > 0) carried the fat loss efficiency GG genotype. The G allele was reported negatively association with BMI (*beta*= -0.0210, $P= 2.29\times10^{-4}$) [30], as well as the trunk fat mass (*beta*= -0.056, $P= 2.59\times10^{-3}$) and waist circumference (*beta*= -0.135, $P= 1.56\times10^{-3}$) in UKB on the Open Targets Genetics [28, 29]. The results indicated that the G allele carriers might have the lower obesity risk and get more benefits on fat loss following exercise, and it's worthy to further research in the future.

The lead SNP rs830970 is located on the intron of the *low-density lipoprotein receptor related protein 2* (LRP2) gene. LRP2 (megalin) is an endocytic receptor expressed on the apical surface of several epithelial cells that internalizes a variety of ligands [31], and plays important roles in the IgA nephropathy [32], atherosclerosis through the renin-angiotensin system [33]. A lacking of LRP2 in the brain endothelial cells may induced obesity by regulating the leptin signaling pathway [34]. Although the rs830970 is a novel SNP, the linkage disequilibrium SNP rs2247506 (r^2=0.88) reported was significantly associated with a prostate cancer risk (FDR P trend^2=0.04) [35]. Moreover, the correlations between plasma cholesterol levels and the variants in LRP2 gene [36] might be a clue to explore the connection between LRP2 polymorphous and the exercise-induced fat mass change.

In the function analysis, the noteworthy biological processes and KEGG pathways would be such as the fat cell differentiation (GO:0045444), Apelin signaling pathway (hsa04371), Insulin secretion (hsa04911). Apelin signaling pathway (hsa04371) has been implicated in obesity and energy metabolism [37-39], and related with the insulin resistance [38]. Higher apelin levels was found in obesity [40], But the association

between apelin and exercise is controversial. Apelin was reported the significantly increasing follow acute high-intensity sprint interval training [41], but long-term Exercise training can't induce the changes in apelin [42]. Basing on our findings, the Apelin signaling pathway related genes may contribute to the fat mass change following exercise training. The effect of apelin signaling pathway and the connection with insulin secretion pathway in exercise training need further research.

Exercise could bring us benefits for both body composition and cardiovascular health [6]. The obesity related traits shown in BMI [43], fat mass, waist circumference [44], Waist-to-height ratio [45] and the blood lipid [46, 47] indicated the risk of cardiovascular or cardiometabolic diseases. Single SNPs explained only a small part of the variance (Top PVE: 5.7%, SNP rs1467243 in FRRS1L gene) in fat mass response to the standardized exercise training. The proportion of variance explained by each SNP is usually low, because the phenotype depend on the effects of multiple genes. To address the low explanatory power of individual SNPs, Polygenic Risk Scores (PRS) are widely used in medical research to assess an individual's susceptibility to diseases [48, 49].and PRS has also been adapted as the PPS in predicting the effect of exercise [14]. According to our findings, the PPS showed an explanation of 28.1% in predicting the exercise-induced fat mass change, especially the threshold scores -9.301 indicated the highest response. The predictive model consisting of the PPS and the phenotypes (the baseline BM, sex and the protocols) would explain 40.3% variance of the fat mass response. The explanation was inconsistent with the models predicting the VO_2max response [18] and heart rate at the fixed load cycling [27] to the standardized exercise training.

One limitation of our study was the wide BMI range of the participants. Specifically, only 24% of the subjects were classified as overweight or obese according to the Chinese BMI standards (Overweight: 24 ≤

BMI < 28; Obese: BMI ≥ 28). Despite this limitation, our study was the first to identify genetic variants underlying fat mass response to exercise in a Chinese population. We elucidated that the PPS derived from ten SNPs, in combination with sex, baseline body mass, and exercise protocols, accounts for 40.3% of the variance in fat mass response to exercise. However, further replication studies are necessary to determine if these findings are applicable in other cohorts, such as those who are overweight or obese.

Conclusion

This is the first study to examine the genomic predictors of fat mass response to the standardized exercise training in a Chinese cohort. The results showed that ten lead SNPs were associated with the fat loss efficient to a 12-week standardized exercise training, and the top single predictor was the SNP rs1467243 ($P = 7.98\times10^{-7}$) in the FRRS1L gene which could explain 5.7% variance of the fat mass response and the lower obesity risk allele G indicate more efficient on exercise-induced fat loss. Moreover, the PPS, which was derived from ten SNPs, combining with the sex, baseline BM and exercise protocols could explain 40.3% of the variance in fat mass response to exercise and importantly the PPS had the greatest contribution. The subjects whose PPS lower than -9.301 would have the high response in exercise-induced fat loss. The genetic contributions to the fat cell differentiation biological process are noteworthy for the further research on fat mass response to exercise training.

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Figure 1. Study design. RT indicated the resistance training. HIIT indicated the High-intensity interval training. GWAS indicated the genome wide association study. PPS indicated polygenic predictor score. SNP indicated the single nucleotide polymorphism.

Figure 2. The distribution of BFM changes following 12 weeks of exercise. Figure 2a illustrates the distribution of BFM changes in the whole cohort, With X axis representing the bin center and the Y axis representing the number of the individuals. Figure 2b shows the percentage change in BFM for subjects in each quartile, separated by exercise. Quartile 1, 2, 3 and 4 indicate the first, second, third, and fourth quartile, respectively.

Figure 3. The Manhattan plot of fat mass response to exercise GWAS results. The significance of the SNPs in 22 autosomes showed in variance colors. The GWAS was performed in the Chinese cohort

Figure 4. The BFM change after exercise in different genotype of the top SNPs. Figure 4a showed the differences between the BFM change in SNP rs7187742 CC, TC and TT carriers. * indicated the BFM change of CC carriers was significantly lower than the TC carriers (*Bonferroni P*<0.05, 95%CI: -7.19~ -0.83); #indicated the BFM change of CC carriers was significantly lower than the TT carriers (*Bonferroni P*<0.05, 95%CI: -21.43~ -1.89).

Figure 4b showed the differences between BFM change in SNP rs1467243 CC, GC and GG carriers. * indicated the subjects with CC genotype had a greater BFM change than the GC carriers (*Bonferroni P*<0.05, 95%CI: 2.50~8.91); #indicated the subjects with CC genotype had a greater BFM change than the GG carriers (*Bonferroni P*<0.05, 95%CI: 3.63~ 25.53).

Figure 4c showed the differences between BFM change in SNP rs10848501 CC, CT and TT carriers. * indicated the subjects with CT genotype had a greater BFM change than the CC carriers (*Bonferroni P*<0.05, 95%CI: 0.48~ 8.08); #indicated the subjects with TT genotype had a greater BFM change than the CC carriers (*Bonferroni P*<0.05, 95%CI: 3.42~11.63).

Figure 5. The KEGG pathway and GO analysis results with the mapping genes. Figure 5a shows the top 35 KEGG pathways related to the fat mass response to exercise. Figure 5b displays the top 5 GO findings related to the fat mass response to exercise.

Figure 6. The PPS between the subjects in different quartile of BFM change. PPS indicated polygenic predictor score. The four sub-groups separated by quartile showed in 1st, 2nd, 3rd and 4th. * indicated the significant differences between the subjects in the 1st Quartile and other quartiles. # indicated the significant differences between the subjects 4th Quartile and other quartiles.

Table 1. The BFM change after 12-week exercise training

Table 2. The lead SNPs of fat mass response to exercise GWAS. SNP indicated the single nucleotide polymorphism. CHR indicated chromosome. MAF indicated minor allele frequency. PVE indicated the proportion of variance in phenotype explained.

Table 3. The validation of top SNPs in Polish cohort.

Table 4. The linear regression of the fat mass response to exercise. PPS indicated the polygenic predictor Score. BM indicated the body mass.

Table 1. The BFM change after 12-week exercise training.

Change range	*Baseline BFM kg*	*Post BFM kg*	*BFM change %*	*Protocols distribution%*	
				HIIT	*RT*
The 1st Quartile: ≤ -9.96%	16.30±8.13	13.38±6.69	-17.94±7.23	67	33
The 2nd Quartile: > -9.96% and ≤-2.12%	15.39±6.24	14.52±5.91	-5.65±2.22	67	33
The 3rd Quartile: > -2.12% and ≤5.16%	16.73±7.20	16.97±7.30	1.53±2.18	56	44
The 4th Quartile: > 5.16%	12.97±5.55	14.47±5.85	12.56±6.42	48	52

Table 2. The lead SNPs of fat mass response to exercise GWAS.

SNP	*CHR*	*Position (GRCh37)*	*Effect Allele*	*MAF*	*Beta*	*P value*	*Nearest Gene*	*PVE*
rs7187742	16	60450246	T	0.2093	5.786	1.50×10^{-7}	RP11-354I13.2	3.60%
rs1467243	9	111913335	G	0.1687	-5.671	7.98×10^{-7}	FRRS1L	5.70%
rs17372207	10	4782651	T	0.1399	-6.105	4.64×10^{-6}	AKR1E2(46kb)	5.00%
rs76937647	7	41330733	A	0.249	-4.109	5.22×10^{-6}	AC005022.1(157kb)	3.10%
rs28629770	15	24008242	T	0.1558	5.471	5.75×10^{-6}	RNU6-741P(14kb)	4.10%
rs2277512	14	91113471	G	0.1925	4.685	5.89×10^{-6}	TTC7B:RP11-1078H9.5	4.50%
rs10848501	12	1610964	C	0.4444	-3.665	6.27×10^{-6}	LINC00942	5.00%
rs111676385	12	46509387	A	0.2798	4.169	8.05×10^{-6}	SLC38A1(67kb)	4.40%
rs830970	2	170161500	T	0.06349	-6.813	8.19×10^{-6}	LRP2	3.10%
rs6056129	20	8784534	G	0.06647	-9.505	8.32×10^{-6}	PLCB1	3.80%

SNP indicated the single nucleotide polymorphism. CHR indicated chromosome. MAF indicated minor allele frequency. PVE indicated the proportion of variance in phenotype explained.

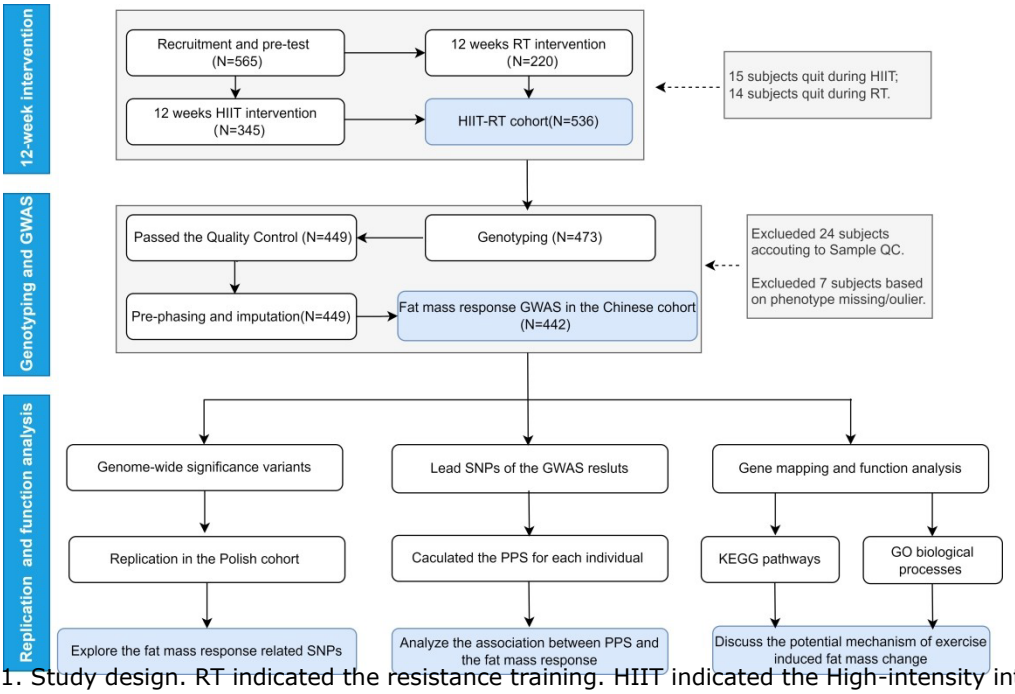
Table 3. The validation of top SNPs in Chinese cohort

SNP	*Effect allele*	*The Chinese cohort*		*The Poland cohort*	
		Beta	*P Value*	*Beta*	*P Value*
rs7187742	T	5.786	1.50×10^{-7}	0.506	0.72
rs1467243	G	-5.671	7.98×10^{-7}	-0.575	0.77
rs28629770	T	5.471	5.75×10^{-6}	3.625	0.43
rs10848501	C	-3.665	6.27×10^{-6}	-1.232	0.40

Table 4. The linear regression of the fat mass response to exercise

Adjusted R^2	*Predictors*	*Unstandardized Coefficients*		*Standardized Coefficients*	*t*	*Partial R^2*	*P Value*	*95.0% CI for Beta 1*	
		Beta 1	*Std. Error*	*Beta 2*				*Lower*	*Upper*
	Constant	6.244	3.045	/	2.050	/	0.041	0.259	12.230
	PPS	0.663	0.046	0.528	14.276	0.281	<0.001	0.571	0.754
0.403	Baseline BM	-0.212	0.039	-0.244	-5.482	0.094	<0.001	-0.288	-0.136
	Protocols	3.438	0.920	0.138	3.739	0.018	<0.001	1.631	5.246
	Sex	3.134	1.086	0.128	2.886	0.010	0.004	1.000	5.268

PPS indicated the polygenic predictor Score. BM indicated the body mass.



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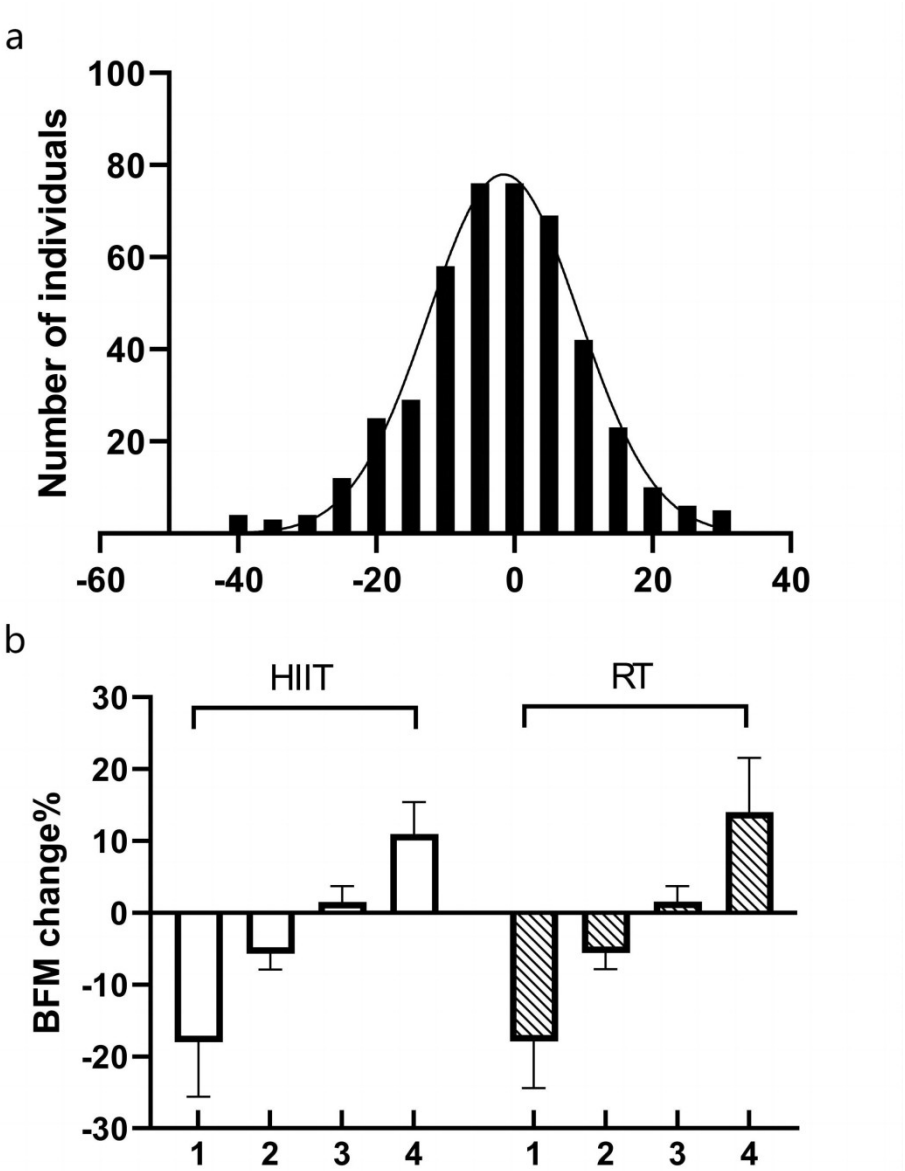

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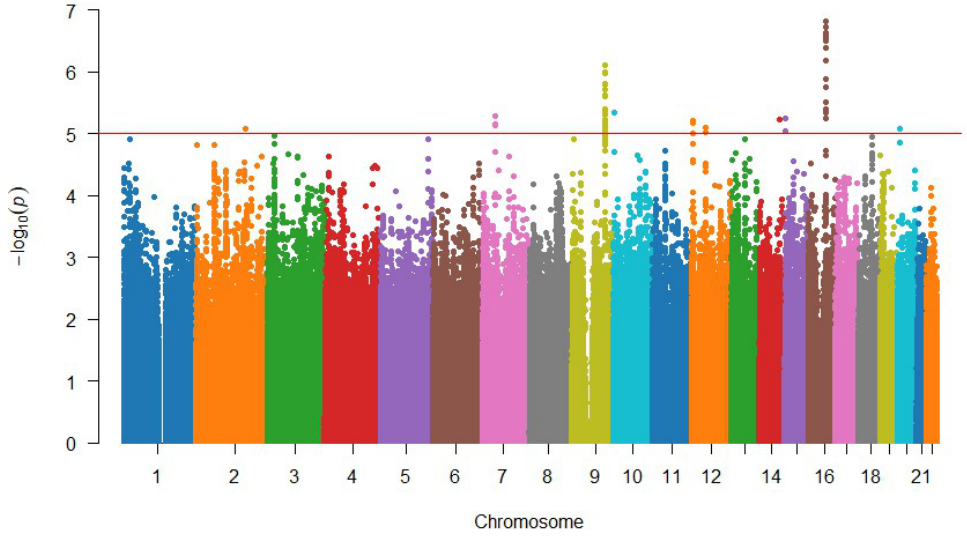

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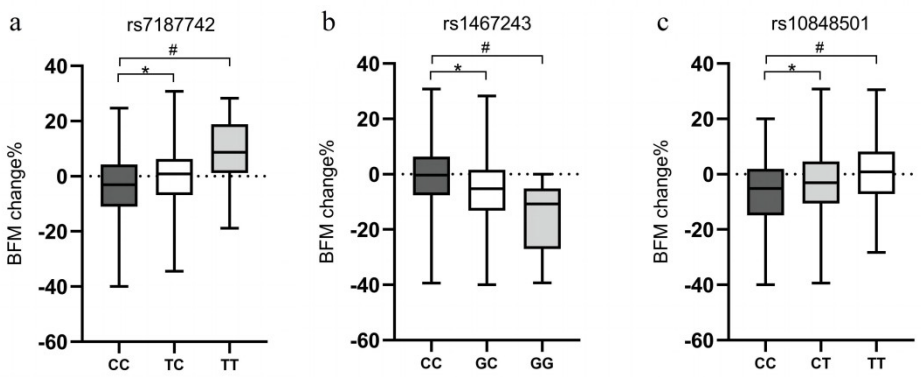

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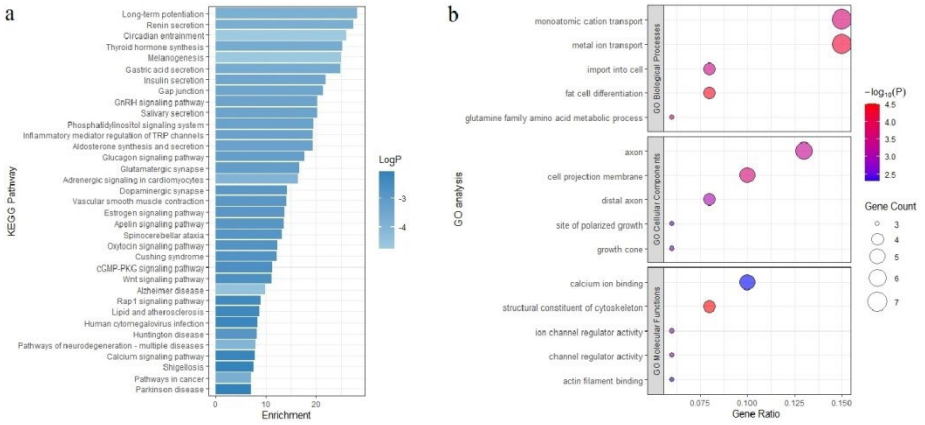

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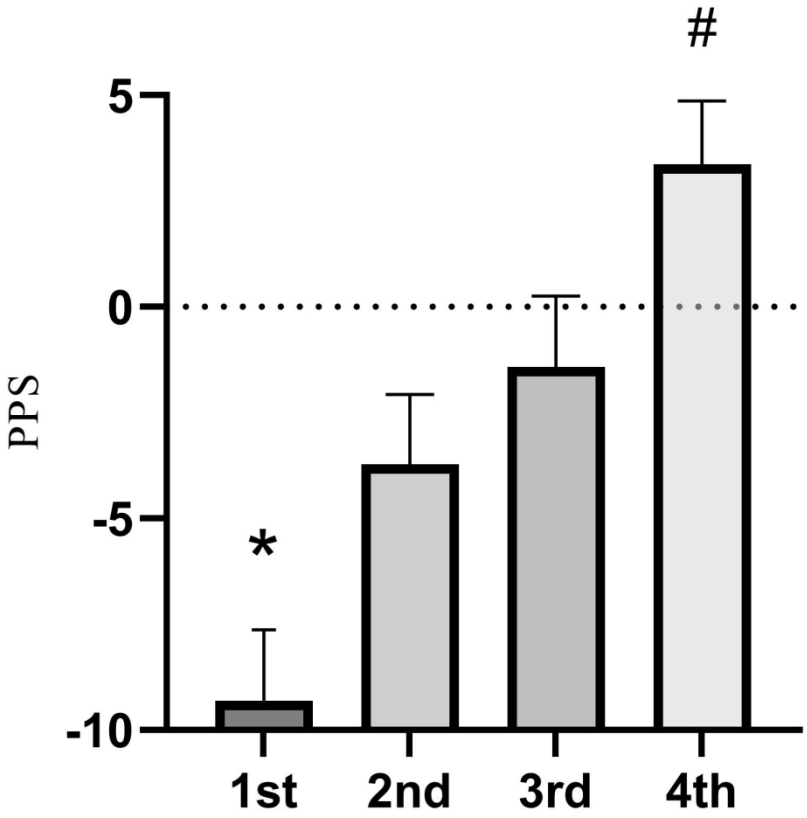

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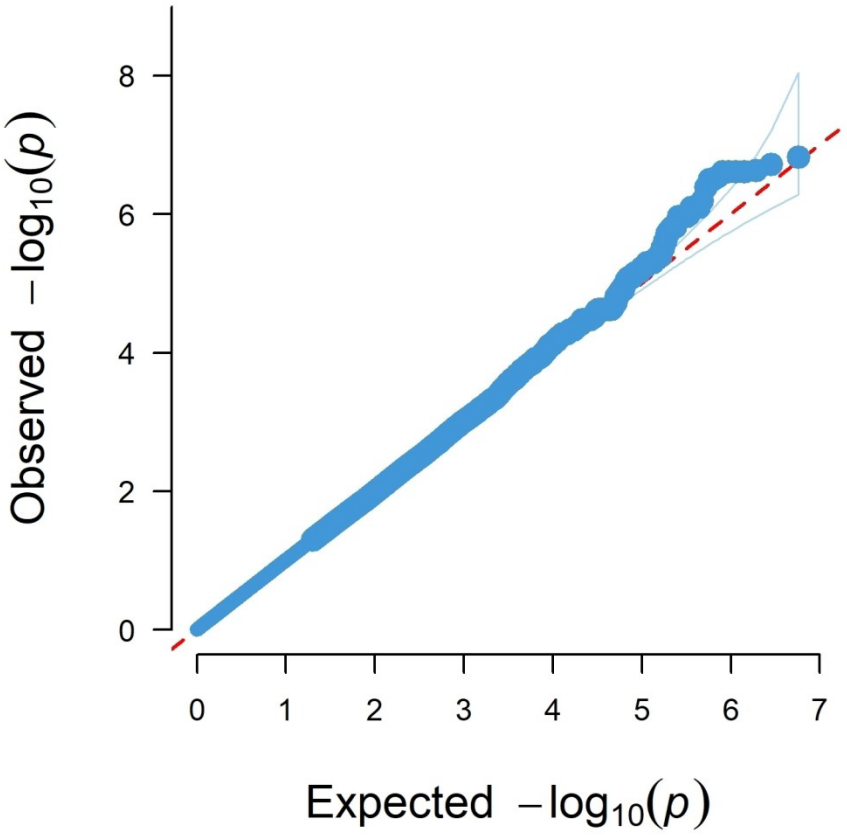
80x79mm (600 x 600 DPI)

Supplemental table S1. The validation of the SNPs reached 1×10^{-4} in Chinese cohort

SNP	CHR	Position (GRCh37)	Allele 1	Allel e2	The Chinese cohort		The Poland cohort		Meta analysis		
					Beta	P-value	Beta	P-value	Zscore	P-value	Direction
rs450092	3	21458362	T	C	4.114	3.00E-05	3.351	3.70E-02	4.664	3.10E-06	++
rs72833505	2	103996803	T	C	-5.637	3.90E-05	-9.661	8.04E-03	-4.877	1.08E-06	--
rs72833506	2	103996888	T	C	5.637	3.90E-05	9.661	8.04E-03	4.877	1.08E-06	++
rs2375764	2	103991582	A	G	-5.605	3.92E-05	-9.661	8.04E-03	-4.876	1.08E-06	--
rs4554332	6	156103246	C	G	-6.788	3.95E-05	-8.247	2.66E-02	-4.671	3.00E-06	--
rs72833512	2	104006277	A	G	5.624	3.98E-05	13.96	6.93E-04	5.222	1.77E-07	++
rs72833515	2	104008156	T	C	5.624	3.98E-05	9.661	8.04E-03	4.873	1.10E-06	++
rs72833517	2	104008282	A	T	-5.624	3.98E-05	-9.661	8.04E-03	-4.873	1.10E-06	--
rs17028779	2	104013264	T	C	-5.624	3.98E-05	-9.661	8.04E-03	-4.873	1.10E-06	--
rs2871499	2	104014351	A	T	-5.624	3.98E-05	-9.661	8.04E-03	-4.873	1.10E-06	--
rs892265	2	104014654	T	C	-5.604	4.27E-05	-9.661	8.04E-03	-4.859	1.18E-06	--
rs17086640	6	156102587	A	G	6.723	4.68E-05	8.247	2.66E-02	4.636	3.56E-06	++
rs4634608	8	94528712	T	C	-3.406	4.94E-05	-3.423	1.07E-02	-4.786	1.70E-06	--
rs17028722	2	103983271	A	G	5.551	5.22E-05	9.661	8.04E-03	4.819	1.44E-06	++
rs72831794	2	103984871	T	C	-5.551	5.22E-05	-9.661	8.04E-03	-4.819	1.44E-06	--
rs17028760	2	103985688	A	G	5.551	5.22E-05	9.661	8.04E-03	4.819	1.44E-06	++
rs72831798	2	103987713	A	G	5.551	5.22E-05	9.661	8.04E-03	4.819	1.44E-06	++
rs72831799	2	103989902	A	G	-5.551	5.22E-05	-9.661	8.04E-03	-4.819	1.44E-06	--
rs72833525	2	104024708	T	C	5.516	6.11E-05	9.661	8.04E-03	4.785	1.71E-06	++
rs10177894	2	104046906	A	G	5.465	6.65E-05	9.661	8.04E-03	4.767	1.87E-06	++
rs17028824	2	104026000	A	G	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs72833527	2	104026144	T	C	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs17028827	2	104027106	A	G	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs17028830	2	104028475	A	G	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs17028837	2	104030418	A	G	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs72833529	2	104032106	A	G	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs145895525	2	104032307	A	G	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs72833531	2	104033577	T	C	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs7567138	2	104039254	A	T	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs10180843	2	104041434	T	C	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs13400209	2	104042000	A	G	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs28406108	2	104042848	A	C	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs13404573	2	104043707	A	C	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs17028872	2	104049356	T	C	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs10496373	2	104049650	T	C	-5.489	6.70E-05	-9.661	8.04E-03	-4.765	1.89E-06	--
rs72833538	2	104051838	T	C	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs13417179	2	104051855	T	C	5.489	6.70E-05	9.661	8.04E-03	4.765	1.89E-06	++
rs28672867	8	94554691	T	G	3.198	8.89E-05	3.833	6.77E-03	4.734	2.20E-06	++
rs10496372	8	94548961	A	G	3.218	8.91E-05	3.833	6.77E-03	4.733	2.21E-06	++

SNP indicated the single nucleotide polymorphism, CHR indicated chromosome.



436x401mm (96 x 96 DPI)