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β-gal staining. Day 1 pups were sacrificed, sliced in two halves along the middle line and fixed in 10% neutrally buffered formalin overnight. Rinse pups three times in detergent buffer (0.1M phosphate buffer, pH7.3, 0.02% Nonidet P40, 0.01% sodium deoxycholate, 5mM EGTA and 2mM $MgCl_2$) and stain pups in staining buffer (0.1M phosphate buffer, pH7.3, 0.02% Nonidet P40, 0.01% sodium deoxycholate, 5mM potassium ferricyanide, 5mM potassium ferrocyanide, 20mM Tris.Cl, pH7.3, 1mg/ml X-gal) at 37°C till color fully develops. Then rinse pups and store in 70% ethanol.

Study population. WHI is a longitudinal national health study that investigates strategies to prevent cardiovascular disease, cancer, diabetes, and fractures in postmenopausal women. Details on the design and enrollment of the WHI are published elsewhere(1). The WHI SNP Health Association Resource (SHARe) included 8,515 AA and 3,642 HA participants aged 50–79 years old who participated in the WHI clinical trials or observational study and for whom genome-wide association study genotyping was conducted and who provided supplemental consent that allowed for data sharing. After excluding the participants with missing genetic data, a total of 8,298 AA and 3,526 HA women were involved in this study. Genome-wide genotyping of the WHI-SHARe participants was performed using the Affymetrix 6.0 array (Affymetrix, Inc, Santa Clara, CA). The genotype data were imputed using MACH with reference panels from the 1000 Genomes (1000G) Project Consortium (Version 3, March 2012 release), which provide near complete coverage of common and low-frequency genetic variation with minor allele frequency ≥ 0.5%.

Obesity cases were those participants who had BMI ≥ 30 kg/m^2 at baseline. Prevalent diabetes cases were identified from self-report of diabetes treatment. Incident diabetes was identified as first-time use of glucose lowering medication (insulin or oral glycemic control agents) or hospitalization for previously unreported diabetes(1).

Quality Control Procedures for imputed SNPs. The imputed SNPs in WHI were filtered out when minor allele frequencies (MAF)< 0.05 or the squared correlations (R^2) between original genotypes and imputed dosages <0.3. SNPs within the genomic region of SNRK (i.e., -30 kb upstream to +30 kb downstream) were further filtered out if linkage disequilibrium (LD) R^2>0.8. Finally, 86 SNPs in AA and 68 SNPs in HA women were included in the statistical analysis.

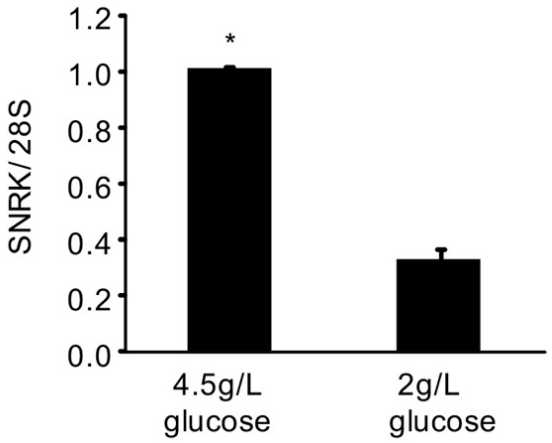
Human Population Statistical Analysis. We used linear model to calculate beta coefficients and 95% confidence intervals (CIs) for single SNP associations with BMI and waist circumference, and logistic regression to calculate odds ratios (ORs) and 95% CIs for single SNP associations with risk of obesity and diabetes. Multivariable models were adjusted for age, geographic region, and four principal components of global ancestry. All models were run separately in AA and HA women. To account for potential false positives because of the multiple comparisons in this study, we calculated the false discovery rate (FDR) by incorporating all *P* values from multiple tests. FDR is defined as the expected proportion of false positives among all significant results. The FDR statistics were obtained for each *P* value, and the FDR statistics with $q <= 0.05$ were considered significant (2). All statistical analyses were conducted with R version 3.2.3 (3). LocusTrack (4) were used for regional visualization of the SNPs association with BMI, waist, and risk of obesity in AA and HA women.

SUPPLEMENTARY DATA

References

1. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19:61-109
2. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the royal statistical society Series B (Methodological) 1995:289-300
3. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria Available: http://wwwr-projectorg/ 2014;
4. Cuellar-Partida G, Renteria ME, MacGregor S. LocusTrack: Integrated visualization of GWAS results and genomic annotation. Source Code Biol Med 2015;10:1

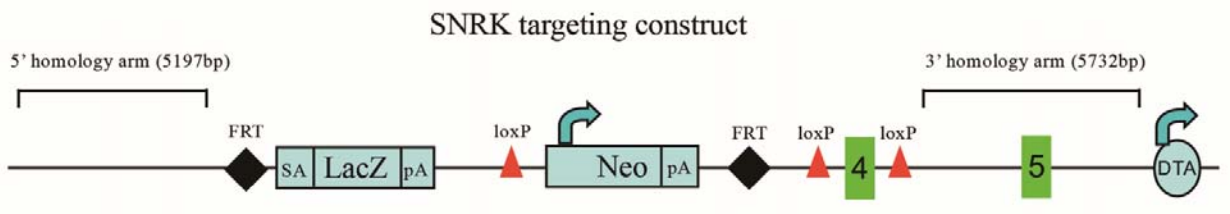
Supplementary Figure 1. Effect of glucose level on SNRK gene expression. **P*<0.05



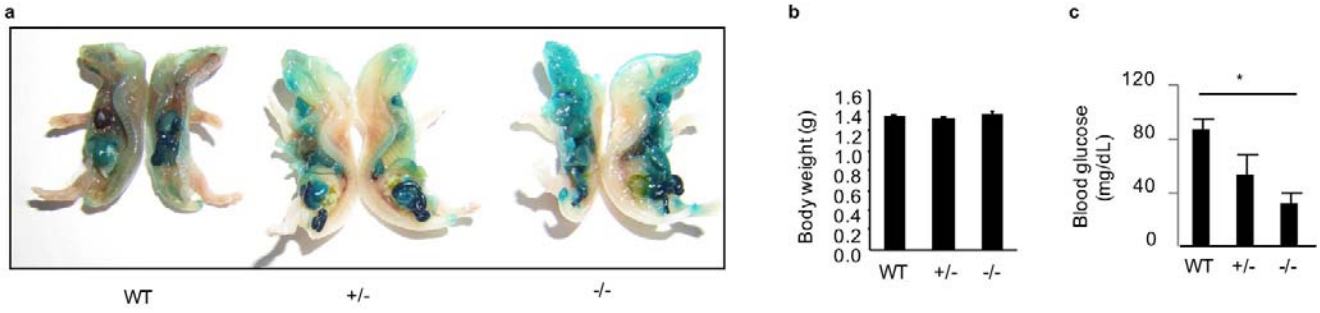
SUPPLEMENTARY DATA

Supplementary Figure 2. Design of SNRK targeting construct.

SA, splice acceptor; LacZ, β-galactosidase gene; Neo, neomycin resistance gene; pA, polyadenylation signal; Neo, neomycin; FRT, Flp recombinase recognition target; loxP, Cre recombinase recognition site; 4, exon 4; 5, exon 5; DTA, diphtheria toxin gene.

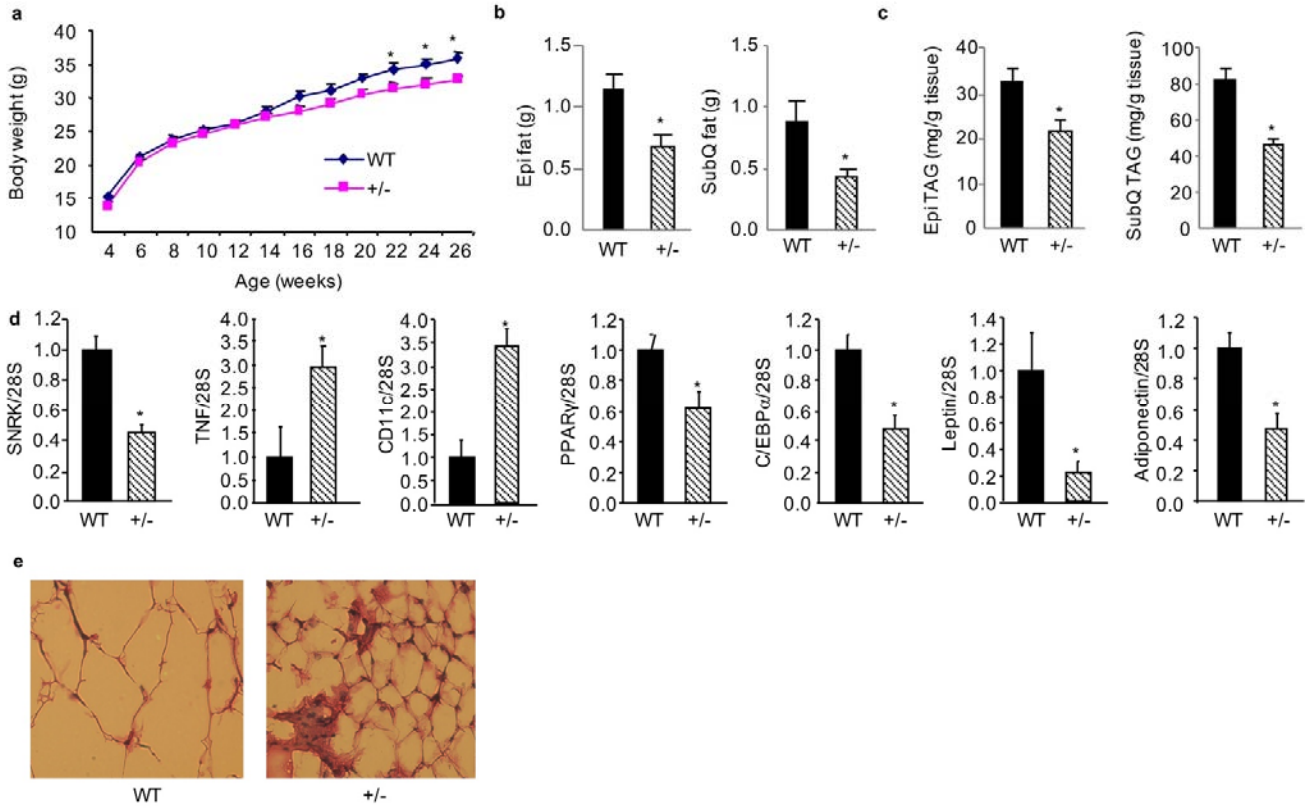


Supplementary Figure 3. SNRK deficient pups.



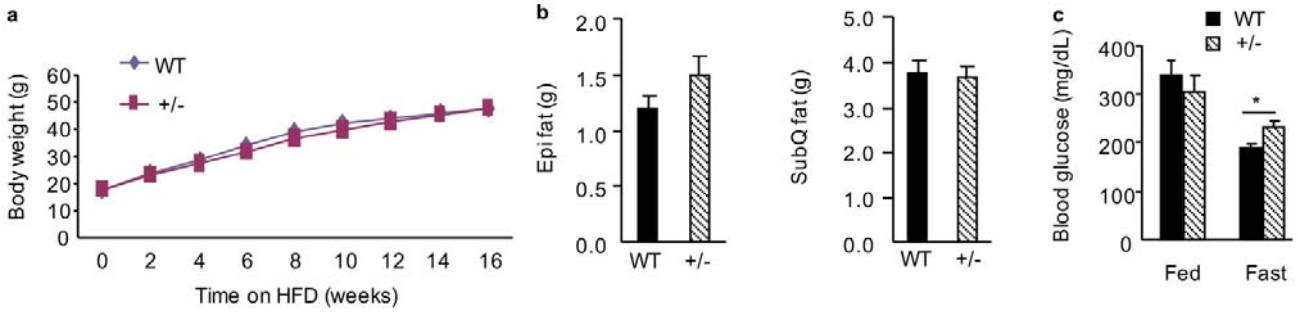
SUPPLEMENTARY DATA

Supplementary Figure 4. Characterization of SNRK heterozygous mice on a chow diet.
(**a**) Growth curve of WT and SNRK$^{+/-}$ male mice on a chow diet (n=6-8 per group). (**b**) Weights of epididymal (Epi) and subcutaneous (SubQ) white adipose tissue (WAT) of WT and SNRK$^{+/-}$ mice (n=6-8 per group). (**c**) Triglyceride (TAG) contents in Epi and SubQ WAT of WT and SNRK$^{+/-}$ mice (n=6-8 per group). (**d**) Gene expression in SubQ WAT of WT and SNRK$^{+/-}$ mice (n=6-8 per group). (**e**) HE staining of subcutaneous WAT from WT and SNRK$^{+/-}$ male mice fed on a chow diet. * P<0.05 as indicated.

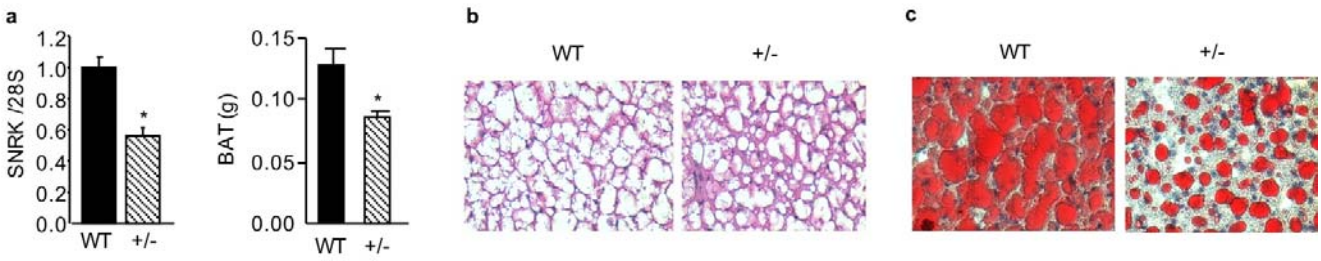


SUPPLEMENTARY DATA

Supplementary Figure 5. Characterization of SNRK heterozygous mice on a high fat diet.
(**a**) Growth curve of WT and SNRK$^{+/-}$ male mice on a high fat diet (HFD) (n=6-7 per group). (**b**) Weights of epididymal (Epi) and subcutaneous (SubQ) white adipose tissue of WT and SNRK$^{+/-}$ male mice on a HFD (n=6-7 per group). (**c**) Blood glucose levels of WT and SNRK$^{+/-}$ male mice on a HFD (n=6-7 per group). * P<0.05 as indicated.

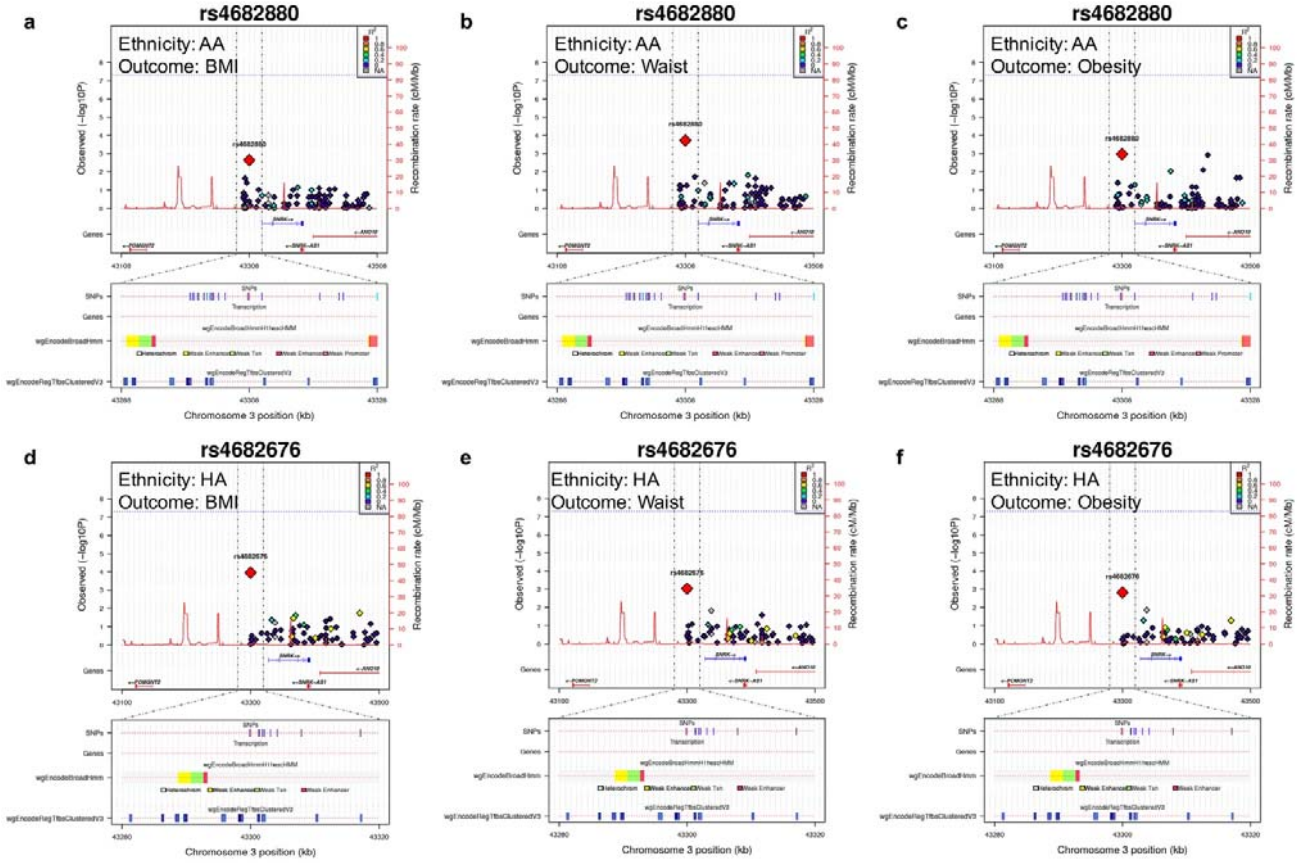


Supplementary Figure 6. Effect of SNRK heterozygosity on brown adipose tissue (BAT).
(**a**) SNRK gene expression in BAT and weights of BAT from WT and SNRK$^{+/-}$ male mice fed on a chow diet (n=6-8 per group). (**b**) HE staining of BAT from WT and SNRK$^{+/-}$ male mice fed on a chow diet. (**c**) Oil red O staining of BAT from WT and SNRK$^{+/-}$ male mice fed on a chow diet. * P<0.05 as indicated.



SUPPLEMENTARY DATA

Supplementary Figure 7. Regional association of the SNRK SNPs with BMI, waist circumference, and risk of obesity in African American (AA) and Hispanic American (HA) women



SUPPLEMENTARY DATA

Supplementary Table 1. Phosphoproteins that have significantly increased phosphorylation level by 50% and more upon SNRK overexpression.

Symbol	Name	Phosphorylation sites	SNRK/GFP ratio	Q Value for SILAC
Signal transduction				
SNRK	SNF-related serine/threonine-protein kinase	S162	16.86	0.03
SNRK	SNF-related serine/threonine-protein kinase	S390	11.02	0.02
ARHGAP17	Rho GTPase-activating protein 17	T730T734T736S739	7.98	0.03
RRAS2	Ras-related protein R-Ras2	S186	6.97	0.04
AHNAK	Ahnak AHNAK nucleoprotein isoform 1	S116	4.92	0.02
Transcription				
Hmga1	MCG120563, isoform CRA_a	S91	34.55	0.02
XRN2	5'-3' exoribonuclease 2	S448	4.85	0.03
HDAC1	**Histone deacetylase 1**	**S393**	**1.72**	0.03
Messenger RNA processing				
HNRPLL	Heterogeneous nuclear ribonucleoprotein L-like	S37	21.18	0.02
HNRNPC	Heterogeneous nuclear ribonucleoproteins C1/C2	S268	7.02	0.04
Translation				
EEF1D	**Eef1d protein**	**S133**	**2.52**	0.01
EEF1D	Eef1d protein	S162	1.87	0.04
Glucose and lipid metabolism				
PDHA1	Pyruvate dehydrogenase E1 alpha 1	S293S300	5.57	0.03
Transport				
MORC2	MORC family CW-type zinc finger protein 2A	S741	7.85	0.04
OSBP	Oxysterol-binding protein	S303	2.27	0.03
Cytoskeleton				
ITGB1	Integrin beta	S1070	153.90	0.03
CGN	Cingulin	S131	1.88	0.04
Cell Cycle				
CCNE2	Cyclin E2	S20	7.24	0.01
PDS5B	Sister chromatid cohesion protein PDS5 homolog B	S1281	6.46	0.02
CEP55	Centrosomal protein of 55 kDa	S428	2.18	0.01
Iron-sulfur cluster assembly				
NUCB1	Nucleobindin-1	S368	7.80	0.02
Miscellaneous				
KRI1	Protein KRI1 homolog	S183S184S188	3.11	0.02
SHROOM2	SHROOM2	S236	1.76	0.05

SUPPLEMENTARY DATA

Supplementary Table 2. Baseline characteristics of African American and Hispanic American women in the WHI-SHARe

	AA	HA
n	8,298	3,526
Age[1], year	61.6 (7.0)	60.3 (6.7)
BMI[1], Kg/m^2	31.1 (6.6)	28.9 (5.8)
Waist[1], cm	91.6 (13.8)	86.7 (12.8)
Obesity, %	49.9	35.8
Diabetes[2], %	30.3	23.4

[1] Data are shown as mean (SD).
[2] Both prevalent and incident cases were included.

SUPPLEMENTARY DATA

Supplementary Table 3. Top 5 associations of common variants in *SNRK* gene with BMI, waist, and risks of obesity and diabetes in African American (AA, *n*=8,298) and Hispanic American (HA, *n*=3,526) women in the WHI-SHARe

Ethinicity	Outcomes	dbSNP ID	Allele[1]	MAF	beta/OR (95% CI)[2]	*P* value	*q* value
AA	BMI	rs4682880	T/C	0.16	0.38 (0.14, 0.62)	0.002	0.19
		rs4682677	C/A	0.06	-0.53 (-0.98, -0.07)	0.02	0.76
		rs9845574	T/G	0.38	-0.25 (-0.48, -0.01)	0.04	0.76
		rs17075583	T/C	0.10	0.28 (-0.02, 0.58)	0.07	0.76
		rs1848069	T/C	0.13	0.24 (-0.03, 0.50)	0.08	0.76
	Waist	rs4682880	T/C	0.16	0.98 (0.46, 1.49)	<0.001	0.01
		rs73831272	C/T	0.22	0.58 (0.11, 1.05)	0.02	0.35
		rs72863618	G/A	0.11	0.72 (0.12, 1.32)	0.02	0.35
		rs1848069	T/C	0.13	0.64 (0.09, 1.20)	0.02	0.35
		rs190271078	A/G	0.11	0.67 (0.03, 1.30)	0.04	0.35
	Obesity	rs4682880	T/C	0.16	1.13 (1.05, 1.22)	0.001	0.05
		rs62250912	G/T	0.06	0.75 (0.63, 0.89)	0.001	0.05
		rs34557672	C/A	0.09	0.82 (0.71, 0.95)	0.01	0.19
		rs17075583	T/C	0.10	1.13 (1.03, 1.24)	0.01	0.19
		rs9881028	T/C	0.37	1.09 (1.01, 1.17)	0.02	0.29
	Diabetes	rs9817430	A/G	0.34	1.10 (1.01, 1.19)	0.02	0.89
		rs56412846	G/A	0.10	0.90 (0.81, 1.00)	0.05	0.89
		rs4234429	T/C	0.06	1.13 (0.99, 1.30)	0.06	0.89
		rs9844641	T/C	0.07	0.91 (0.81, 1.02)	0.09	0.89
		rs4682676	G/A	0.07	1.10 (0.98, 1.24)	0.10	0.89
HA	BMI	rs4682676	G/A	0.07	-2.81 (-4.24, -1.39)	<0.001	0.004
		rs4234429	T/C	0.06	-1.72 (-3.15, -0.29)	0.02	0.27
		rs4682881	C/A	0.07	-1.69 (-3.15, -0.22)	0.02	0.27
		rs2372373	T/G	0.06	-1.86 (-3.58, -0.14)	0.03	0.27
		rs34027772	C/T	0.05	-0.85 (-1.65, -0.05)	0.04	0.27
	Waist	rs4682676	G/A	0.07	-5.31 (-8.45, -2.17)	0.001	0.02
		rs181229667	A/G	0.05	-2.97 (-5.37, -0.57)	0.02	0.20
		rs9818582	A/G	0.27	-0.83 (-1.57, -0.10)	0.03	0.23
		rs116896819	C/A	0.07	0.85 (-0.11, 1.80)	0.08	0.25
		rs4682880	T/C	0.16	-1.63 (-3.48, 0.21)	0.08	0.25
	Obesity	rs4682676	G/A	0.07	0.44 (0.26, 0.73)	0.002	0.07
		rs181229667	A/G	0.05	0.62 (0.42, 0.91)	0.01	0.31
		rs1395373	C/T	0.11	0.70 (0.49, 1.00)	0.05	0.53
		rs4234429	T/C	0.06	0.61 (0.37, 1.00)	0.05	0.53
		rs34027772	C/T	0.05	0.79 (0.60, 1.05)	0.11	0.53
	Diabetes	rs4682676	G/A	0.07	0.52 (0.31, 0.87)	0.01	0.79
		rs4396868	A/G	0.32	0.88 (0.76, 1.01)	0.06	0.83
		rs6793392	G/C	0.30	1.11 (0.99, 1.24)	0.06	0.83

	rs4682880	T/C	0.16	0.75 (0.55, 1.03)	0.08	0.83
	rs114398053	A/G	0.08	1.59 (0.95, 2.66)	0.08	0.83

[1] Major (Reference)/Minor Allele.
[2] MAF, Minor allele frequency.
[3] The associations of SNPs with BMI and waist are shown as beta (95% CI). The associations of SNPs with risks of obesity and diabetes are shown as OR (95% CI).