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Susceptibility Variants for Waist Size in Relation to Abdominal, Visceral and Hepatic Adiposity in Postmenopausal Women

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Abstract

Genome-wide association studies (GWAS) have identified common genetic variants that may contribute specifically to the risk of abdominal adiposity, as measured by waist circumference or waist-to-hip ratio. However, it is unknown whether these genetic risk factors affect relative body fat distribution in the abdominal visceral and subcutaneous compartments. The association between imaging-based abdominal fat mass and waist size risk variants in the *FTO*, *LEPR*, *LYPLAL1*, *MSRA*, *NRXN3*, and *TFAP2B* genes was investigated. A cross-sectional sample of 60 women were selected among study participants of Multiethnic Cohort, who were of ages 60–65 years, of European or Japanese descent, and with body mass index (BMI) between 18.5 and 40 kg/m². Dual energy X-ray absorptiometry (DXA) and abdominal magnetic resonance imaging (MRI) scans were used to measure adiposity. After adjustments for age, ethnicity and total fat mass, the *FTO* variants showed an association with less abdominal subcutaneous fat and a higher visceral-to-subcutaneous abdominal fat ratio, with the variant rs9941349 showing significant associations most consistently ($p=0.003$ and 0.03 , respectively). Similarly, the *LEPR* rs1137101 variant was associated with less subcutaneous fat ($p=0.01$) and a greater visceral-to-subcutaneous fat ratio ($p=0.03$) and percent liver fat ($p=0.007$). *MSRA* rs545854 variant carriers had a lower percent leg fat. Our findings provide initial evidence that some of the genetic risk factors identified for larger waist size may also contribute to disproportionately greater intra-abdominal and liver fat distribution in postmenopausal women. If replicated, these genetic variants may be incorporated with other biomarkers to predict high-risk body fat distribution.

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Keywords

body composition; central obesity; fatty liver; single nucleotide polymorphisms; liver fat; race/ethnicity; subcutaneous adipose tissue; visceral adipose tissue

INTRODUCTION

Obesity is the leading cause of diabetes (1) and cardiovascular diseases (2) and is growing in importance as a risk factor for cancer (3). Obesity is rising as a cause of overall cancer incidence to surpass smoking (3–5) and may curtail some of the life expectancy gained from smoking cessation (5). In particular, fat deposition in the abdominal region, often assessed by measuring waist circumference or waist-to-hip ratio, shows a stronger and/or independent association with risk of metabolic diseases, compared to that of overall adiposity measured by body mass index (BMI; kg/m²) (6–11). Furthermore, visceral adiposity in the intra-abdominal region has been associated with higher risk of metabolic disorders compared to abdominal subcutaneous adiposity (12–14). Therefore, identifying determinants of abdominal and visceral adiposity is of high priority. To date, only a few risk factors have been identified for abdominal adiposity, including advancing age, male sex and non-white ethnicities (15), leaving much of the individual variability unexplained.

Family and twin studies have suggested that the majority of variance in whole-body and intra-abdominal fat distribution is heritable (16, 17). Recent large-scale genome-wide association studies (GWAS) have identified several risk variants that are specifically associated with a greater waist circumference or waist-to-hip ratio (18, 19). However, the genetic risk variants identified from these GWAS have rarely been examined in relation to imaging-based measurements of body fat distribution.

In a recent study of a subgroup of the Multiethnic Cohort, significantly greater proportional adiposity in the trunk and visceral regions was observed among Japanese American women, compared to white women with comparable levels of total adiposity (20). The current study investigated whether the GWAS-identified risk variants for waist size were associated with greater proportional abdominal adiposity measured by dual energy X-ray absorptiometry (DXA), and with greater visceral or liver adiposity based on abdominal magnetic resonance imaging (MRI).

MATERIALS AND METHODS

Study Subjects

As described elsewhere (20), women were recruited for a detailed body composition study. They were a random sample of Multiethnic Cohort Study participants (21, 22) who were residents of Oahu, Hawaii, were 60–65 years of age as of September 2009 and had reported that both parents were either Japanese or white. Of the 218 women who were randomly selected, 46 were excluded based on current smoking, use of medications (chemotherapy, insulin, or weight-loss drugs), a substantial weight change (> 20 pounds in the past six months) or soft or metal implants/objects in the body, which could bias the body composition estimates or put subjects at risk in the magnetic field. An additional 98 women were unavailable or unwilling. Among the 74 remaining women (34%), 60 women (30 Japanese American, 30 whites) were selected based on BMI categories to obtain a similar distribution of BMI by ethnicity.

Participants underwent anthropometric measurements, a whole-body DXA scan and a fasting venous blood collection at the University of Hawaii Clinical Research Center. Forty-

eight of the 60 women also agreed to participate in an abdominal MRI scan at the University of Hawaii and Queen's Medical Center (UH-QMC) MR Research Center. The Institutional Review Boards of UH and QMC approved the study protocol, and all participants signed an informed consent.

Body Fat Distribution

Anthropometric measurements included standing and sitting heights, weight, and waist and hip circumferences. A whole-body DXA scan (GE Lunar Prodigy, Madison, WI) was performed to measure lean body mass and fat mass in total and in the trunk, arms and legs (23), from which percent total fat (total fat mass divided by total body mass) was derived. Percent of total fat in the trunk (percent trunk fat) and the trunk-periphery fat mass ratio, calculated by dividing the trunk fat mass by the sum of fat mass in the arms and legs, were used as indicators of fat distribution in the abdominal relative to the peripheral regions. A subset of 20 Japanese American and 28 white women completed an abdominal MRI scan within a median interval of 7.6 weeks after the DXA scan. As described in detail (20), the women were scanned with a 3 Tesla TIM Trio scanner (Siemens Medical Systems, Erlangen, Germany), in a supine position, with their abdominal area covered with the body matrix coil. Each subject's cross-sectional image at L4-L5 spine position was analyzed to determine the total adipose and visceral adipose tissue (VAT; intra-abdominal fat) areas. The subcutaneous adipose tissue (SAT) area was then calculated by subtracting the visceral fat area from the total fat area at L4-L5. In addition, the VAT and SAT areas as percentages of MRI total abdominal area at L4-L5, as well as visceral-to-subcutaneous fat ratio, were assessed. In addition, the relative fat content of the liver was estimated from the analysis of a circular region (15–25 cm²) in the lateral portion of the right lobe of the liver (24).

Genotyping

Genomic DNA was purified from blood buffy coat stored at –80°C. Eleven single nucleotide polymorphisms (SNPs) in five genes/loci (seven SNPs in *FTO* and one each in *LYPLAL1*, *MSRA*, *NRXN3*, and *TFAP2B*) were considered in the current analysis (Table 1), based on the GWAS findings for waist size available as of August 2010 (18, 19). In addition, *LEPR* rs1137101 was included based on our earlier observation of its association with trunk-to-periphery fat ratio in multiethnic adolescent girls in Hawaii [Vijayadeva et al., personal communication]. Genotyping of all 60 samples, blinded to the subject characteristics, was conducted at the University of Hawaii Cancer Center Genomics Shared Resource laboratory: the GWAS variants were typed using the TaqMan OpenArray system (Applied Biosystems, Foster City, CA) and the *LEPR* variant, using the standard TaqMan allelic discrimination assay. Quality control samples (12%) had consistent genotype calls for all SNPs. In addition, >99% concordance was observed for all GWAS SNPs for 375 HapMap samples that were assayed for quality assurance as part of another study (25). All genotype distributions were consistent with Hardy-Weinberg equilibrium within each ethnic group [*p*-value for χ^2 test >0.025 for two ethnic groups; HaploView (Broad Institute, Cambridge, MA)]. All *FTO* variants were in linkage disequilibrium (LD): the *r*² range was 64–100% in Japanese Americans and 86–100% in whites.

Statistical Analysis

All analyses were performed using the SAS Statistical Software, version 9.2. The main analysis included comparisons by genotype of adiposity indicators for: total or overall adiposity (BMI and DXA percent total fat), central or abdominal adiposity (waist circumference, waist-to-hip ratio, DXA percent trunk fat and trunk-to-periphery fat ratio), peripheral adiposity (DXA percent leg fat and DXA percent arm fat), the distribution of abdominal fat (MRI VAT and SAT absolute and relative areas) and hepatic adiposity (MRI percent liver fat). Mean adiposity values were compared across genotypes as nominal

categories using analysis of covariance (ANCOVA), and a p for trend was assessed using an additive model. The model assumptions were met for all models, although log-transformation was required for MRI percent liver fat. Models for total and percent regional adiposity were adjusted for age and ethnicity. Models for MRI abdominal fat distribution were additionally adjusted for DXA total fat mass since the study objective was to compare the proportional visceral, subcutaneous and hepatic adiposity at similar levels of overall adiposity and because regional adiposity is positively correlated with total body fat. In our study, visceral fat (Spearman correlation coefficient, $r=0.74$; $p<0.0001$), abdominal subcutaneous fat ($r=0.84$; $p<0.0001$) and liver fat ($r=0.31$; $p=0.03$) were significantly correlated with total body fat mass. A nominal level of $\alpha=0.05$ was used for statistical significance.

RESULTS AND DISCUSSION

Allele frequencies among white women in the study (Table 1) were similar to those observed in previous studies conducted in populations of European descent (18, 19). In Japanese American women, allele frequencies for the *FTO* and *LEPR* obesity risk variants were lower compared to white women, whereas the *NRXN3* variant was monomorphic, in agreement with the HapMap data on Japanese and Han Chinese (<http://hapmap.ncbi.nlm.nih.gov/>). Selected characteristics of the study participants are presented in Table 2. By study design, women of Japanese vs. white ancestry were of equal numbers and of similar age and BMI distribution. Women with MRI data were not significantly different from women who declined the MRI with regard to age, percent total fat, or trunk-to-periphery fat ratio (data not shown).

None of the *FTO* risk variants examined was associated with waist circumference (or waist-to-hip ratio; data not shown) or percent body fat overall and in the trunk or legs (Table 3). However, all seven *FTO* risk variants showed a significant association with smaller abdominal SAT area adjusted for total fat mass, and six of them also with lower abdominal SAT area adjusted for total fat mass. Two of these SNPs (rs9930506, rs9941349) were in turn associated with a greater visceral-to-subcutaneous fat ratio, with the other variants showing a non-significant trend in the same direction. The genetic effects appeared dose-dependent on the number of risk alleles for absolute and relative SAT areas but recessive for VAT area and visceral-to-subcutaneous fat ratio. Despite the positive relation to greater visceral adiposity, six *FTO* variants had borderline to significant associations with lower percent liver fat adjusted for total fat. Those who carried no risk allele for waist size variants had higher percent liver fat compared to carriers of one or two risk alleles, with mean percent liver fat values above the cutoff point of 5.5% for diagnosis of fatty liver (26, 27).

Among the non-*FTO* variants, the *LEPR* rs1137101 variant showed a significant association possibly in a recessive manner with a smaller area and lower percentage of abdominal SAT, a higher visceral-to-subcutaneous fat ratio and higher percent liver fat (Table 3). Carriers of the *MSRA* rs545854 risk allele tended to have significantly lower percent leg fat and a trend towards higher percent trunk fat, a higher trunk-periphery fat ratio and higher percent visceral fat area adjusted for total fat. The *TFAP2B* rs987237 variant showed significant associations with greater central and visceral adiposity. However, the associations of the *TFAP2B* variant were largely driven by the sole individual with the homozygous variant genotype. The *LYPLAL1* and *NRXN3* variants did not show any significant relations to regional fat distribution. When the *FTO* rs9941349 and *LEPR* rs1137101 variants, which showed an association for disproportionate intra-abdominal fat distribution, were modeled simultaneously, both of their associations with subcutaneous fat, visceral-to-subcutaneous fat ratio and liver fat remained significant. A similar analysis for liver fat showed an attenuation of the association of the *FTO* rs9941349 (data not shown).

The previously reported associations of ethnicity with central and visceral adiposity (20) remained significant following adjustment for each genetic variant (data not shown). For example, Japanese Americans had a higher waist-to-hip ratio (0.97 vs. 0.89; $p=0.0001$), a higher trunk-periphery fat ratio (1.42 vs. 1.09; $p=0.005$) and greater percent visceral fat (26.3% vs. 16.9%; $p=0.002$) in comparison to whites after adjustment for the *FTO* rs9941349 and *LEPR* rs1137101 variants. The power was limited to compare the SNP-adiposity associations stratified by ethnicity: stratified results reached borderline significance in whites only for the *FTO* or *LEPR* variant. For the joint effects of the *FTO* rs9941349 and *LEPR* rs1137101 variants, carriers of 2 to 4 risk alleles had non-significantly greater abdominal, visceral and hepatic adiposity in both Japanese American and white women (data not shown).

Variants in the *FTO* gene have been most consistently and strongly associated in GWAS with BMI or body weight (28–32) and waist size (18, 19, 33). In the CHARGE consortium study, about 50 correlated variants in the *FTO* gene ranked the highest for correlation with waist-to-hip ratio, followed by variants in other genes (19). Our study included the *FTO* SNP (rs1558902) reported to be most significantly associated with waist-to-hip ratio ($p=4.6E-19$) and 6 other correlated SNPs ($p<1.6E-10$) (19). However, there was no association between these *FTO* variants and indicators of central adiposity, namely, waist size, percent trunk fat and trunk-to-periphery fat ratio. This may be due in part to our insufficient power to detect small effects that were discernible in large-scale GWA studies: estimated per risk-allele increase in waist circumference was 0.73cm for *FTO* (rs9939609), 0.43cm for *MSRA* (rs7826222), 0.65cm for *NRXN3* (rs10146997) and 0.49cm for *TFAP2B* (rs987237), and the difference in waist-to-hip ratio explained by the *LYPLAL1* risk variant (rs2605100) was 0.0014 (18, 19). It is plausible that the *FTO* variants influence intra-abdominal fat distribution more directly than overall waist size. For example, the relative difference by rs9941349 genotypes was much greater for SAT than for waist circumference in our study.

The GWAS-identified SNPs for waist size have rarely been examined in relation to imaging-based body fat distribution. Studies of European whites (34, 35) and Hispanic Americans (36) found that *FTO* variants (including rs1421085 and 6 other closely linked SNPs) were associated positively with BMI (34–36) and SAT at L4-L5 (35, 36) but not significantly with VAT (34–36) or liver fat (34). A study of Japanese adults reported that carriers of *FTO* variants (rs1421085 and rs1558902) had lower absolute areas for both VAT and SAT compared to non-carriers, with no significant differences in fat areas detected by the variants in *LYPLAL1*, *MC4R*, *MSRA* or *TFAP2B* (37). However, these studies did not adjust their measurements of intra-abdominal fat contents (VAT, SAT, visceral-to-subcutaneous fat ratio and liver fat) for total body fat, and therefore, did not demonstrate *disproportionate* fat distribution by genotypes. Since both absolute visceral and subcutaneous fat contents are significantly positively correlated with total body fat, an unadjusted association of the absolute area or mass of the intra-abdominal fat compartments does not offer support for a genetic effect on fat distribution beyond an effect on total adiposity. One study that examined the absolute SAT area difference by *FTO* variants and adjusted for BMI, as a proxy for total fat, reported an attenuation of the unadjusted positive association (35). Therefore, our total fat-adjusted findings provide initial evidence that suggests the existence of specific genetic effects on fat distribution.

In our study, the rs1137101 variant in the leptin receptor (*LEPR*) gene was also examined in addition to the GWAS-identified risk variants. Previously, three *LEPR* variants in high LD, including rs1137101 [a Gln223Arg substitution (Q223A)], have been associated with body fat distribution among European white women, even after adjustment for total fat (38). Specifically, total fat-adjusted hip circumference, total abdominal fat area and subcutaneous

fat area differed by *LEPR* variants, especially among postmenopausal women (38). Our results were similar to these past findings.

How these genetic variants could contribute to fat accumulation in specific depots is not clear. *FTO* expression was observed to be three-fold higher in SAT compared to VAT in humans (39), which may suggest different associations for its genetic variants. Similarly, common variants in *LEPR* may reduce the effects of its ligand, leptin, an adipocyte-secreted hormone and well-established regulator of body weight (40–42). The compromised leptin activity may affect the metabolism of the subcutaneous adipocytes more than their visceral counterparts as the former secrete more leptin and react more sensitively to the paracrine activity of leptin (43, 44), potentially leading to a failure to accumulate fat in SAT and redistribution to VAT.

Due to cost, this preliminary study had a relatively small sample size, which limited power for stratified analyses by ethnicity or by total adiposity levels. Thus, the significant findings could reflect chance. Another limitation of this study is that the estimation of VAT and SAT was based on the cross-sectional areas at L4-L5. Although this inter-vertebral level has been examined most commonly and has shown a good correlation with volumetric measurements (45), measurements at 5–10cm above L4-L5 may better reflect total volumes and the associated metabolic risks according to recent studies (46, 47). In future studies, it would be desirable to also examine these associations in men and in additional ethnic groups. Future research also needs to examine an expanded list of risk variants, to include recent GWAS results (33). The strengths of our analysis included the adjustment for total fat mass, which allowed testing the effect of these variants on fat topography independent of their effects on overall adiposity.

CONCLUSIONS

While replications are warranted, these preliminary data suggest that some of the genetic variants associated with waist size may contribute to greater fat deposition in the visceral vs. subcutaneous compartment of the abdomen and may also influence ectopic lipid storage in the liver. Our findings add to the existing evidence that people exhibit specific susceptibility to abdominal and intra-abdominal fat deposition regardless of overall body fat levels. In this era of personalized medicine, intervention strategies for weight loss and maintenance may also need to be specified on abdominal adiposity since it contributes to greater metabolic risks. Such individuals might be identified by measuring biomarkers (including genetic variants) specific to high-risk fat depots.

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Table 1

Genetic risk variants for waist size and allele frequency

SNP	Nearest Gene	Gene Name	Location	Reference Allele	Risk Allele	Risk Allele Frequency (%)		
						All	Japanese American	White
rs1121980	<i>FTO</i>	fat mass and obesity associated	chr. 16 52366748	G	A	32.2	17.2	46.7
rs1421085	<i>FTO</i>	fat mass and obesity associated	chr. 16 52358455	T	C	31.9	16.1	46.7
rs1558902	<i>FTO</i>	fat mass and obesity associated	chr. 16 52361075	T	A	31.4	15.5	46.7
rs3751812	<i>FTO</i>	fat mass and obesity associated	chr. 16 52375961	G	T	30.5	13.8	46.7
rs9930506	<i>FTO</i>	fat mass and obesity associated	chr. 16 52387966	A	G	32.2	17.2	46.7
rs9939609	<i>FTO</i>	fat mass and obesity associated	chr. 16 52378028	T	A	29.7	13.8	45.0
rs9941349	<i>FTO</i>	fat mass and obesity associated	chr. 16 52382989	C	T	31.4	17.2	45.0
rs1137101	<i>LEPR</i>	leptin receptor	chr. 1 65831101	G	A	34.8	10.3	61.1
rs2605100	<i>LYPLAL1</i>	lysophospholipase-like 1	chr. 1 217710847	A	G	76.3	84.5	68.3
rs545854	<i>MSRA</i>	methionine sulfoxide reductase	chr. 8 9897490	C	G	35.6	39.7	31.7
rs10146997	<i>NRXN3</i>	neurexin 3	chr. 14 79014915	A	G	17.8	0	35.0
rs987237	<i>TFAP2B</i>	transcription factor AP-2 beta	chr. 6 50911009	A	G	24.6	29.3	20.0

Table 2

Characteristics of participating women

	Mean (Standard Deviation) or N (%)
Age, yrs	63.4 (1.37)
Ethnicity, n (%)	
Japanese American	30 (50%)
White	30 (50%)
Weight, kg	66.3 (12.6)
Height, cm	157.5 (5.3)
Body Mass Index (BMI), kg/m ²	26.7 (4.9)
Waist circumference at the navel, cm	94.9 (14.4)
Hip circumference, cm	101.9 (10.4)
Smoking history, n (%)	
Never	37 (62%)
Former	23 (38%)

Table 3

Body fat distribution by genotype for waist size variants among white and Japanese American women*

Genotype (n)	Waist (cm)	% Total Fat	% Trunk Fat	% Leg Fat	Trunk/Periphery Fat	Visceral Fat Area (cm ²)	% Visceral Fat Area	Subcutaneous Fat Area (cm ²)	% Subcutaneous Fat Area	Visceral/Subcutaneous Fat	% Liver Fat
<i>FTO</i> , rs1121980											
GG (27)	92.6	38.9	53.2	33.6	1.3	134	20.7	220	35.1	0.63	6.5
GA (26)	98.0	42.2	53.3	34.1	1.3	138	20.2	193	30.9	0.72	3.5
AA (6)	94.0	41.3	50.6	35.9	1.1	159	22.6	134	23.4	1.24	4.7
<i>P</i> trend	0.47	0.31	0.60	0.71	0.66	0.81	0.76	0.007	0.02	0.05	0.05
<i>FTO</i> , rs1421085											
TT (26)	90.4	38.0	52.9	34.0	1.3	137	22.0	213	34.5	0.70	7.2
TC (27)	98.7	42.4	53.3	33.9	1.3	136	19.9	192	30.7	0.70	3.5
CC (5)	95.4	42.9	49.7	36.4	1.1	154	20.1	124	22.6	1.22	4.3
<i>P</i> trend	0.15	0.10	0.47	0.68	0.56	0.91	0.69	0.01	0.05	0.13	0.01
<i>FTO</i> , rs1558902											
TT (27)	91.4	38.3	53.2	33.8	1.3	134	21.5	217	34.9	0.67	6.6
TA (27)	98.9	42.4	53.4	33.9	1.3	139	20.2	194	30.9	0.71	3.6
AA (5)	95.7	43.1	49.8	36.3	1.1	156	20.3	127	22.8	1.22	4.3
<i>P</i> trend	0.22	0.13	0.49	0.67	0.57	0.89	0.87	0.01	0.04	0.13	0.05
<i>FTO</i> , rs3751812											
GG (28)	92.3	38.6	53.4	33.5	1.3	136	21.6	220	34.9	0.66	6.5
GT (26)	97.7	42.3	53.4	33.9	1.3	138	20.0	195	31.1	0.71	3.5
TT (5)	97.7	43.5	48.8	37.9	1.1	153	20.7	111	21.0	1.30	4.3
<i>P</i> trend	0.48	0.19	0.29	0.32	0.41	0.93	0.81	0.001	0.01	0.06	0.04
<i>FTO</i> , rs9930506											
AA (26)	92.4	38.9	53.0	33.7	1.3	130	20.0	224	35.6	0.59	6.1
AG (28)	97.3	41.9	53.3	34.0	1.3	140	20.8	192	30.8	0.74	3.7
GG (5)	97.8	42.6	50.9	35.9	1.2	165	22.0	121	21.7	1.34	5.3
<i>P</i> trend	0.54	0.34	0.72	0.75	0.76	0.73	0.75	0.002	0.008	0.02	0.14

Genotype (n)	Waist (cm)	% Total Fat	% Trunk Fat	% Leg Fat	Trunk/Periphery Fat	Visceral Fat Area (cm ²)	% Visceral Fat Area	Subcutaneous Fat Area (cm ²)	% Subcutaneous Fat Area	Visceral/Subcutaneous Fat	% Liver Fat
<i>FTO</i> , rs9939609											
TT (28)	92.3	38.5	53.5	33.5	1.3	136	21.6	220	34.9	0.66	6.5
TA (27)	97.4	42.1	53.1	34.2	1.3	138	20.2	192	30.8	0.72	3.5
AA (4)	100.0	45.2	50.0	36.6	1.1	160	19.8	107	20.4	1.35	4.9
<i>P</i> trend	0.46	0.14	0.61	0.65	0.66	0.87	0.83	0.003	0.02	0.07	0.03
<i>FTO</i> , rs9941349											
CC (27)	92.5	38.9	53.2	33.6	1.3	134	20.7	220	35.1	0.63	6.4
CT (27)	97.3	42.0	53.2	34.1	1.3	138	20.3	193	30.9	0.72	3.5
TT (5)	97.7	42.6	50.9	35.9	1.2	164	22.7	122	21.8	1.34	5.3
<i>P</i> trend	0.54	0.32	0.73	0.74	0.76	0.77	0.78	0.003	0.01	0.03	0.03
<i>LEPR</i> , rs1137101											
GG (31)	94.7	40.9	52.2	34.7	1.2	117	18.5	191	32.6	0.62	3.6
GA (11)	92.0	38.7	51.1	35.9	1.2	125	20.2	236	36.7	0.60	4.0
AA (14)	97.8	41.6	55.9	32.0	1.4	185	25.1	169	26.3	1.11	8.4
<i>P</i> trend	0.64	0.57	0.15	0.26	0.27	0.09	0.06	0.01	0.02	0.03	0.007
<i>LYPLAL1</i> , rs2605100											
AA (3)	82.1	40.2	50.6	36.3	1.1	101	18.4	222	40.7	0.54	4.0
AG (22)	98.4	41.7	53.0	34.2	1.3	125	19.9	195	32.0	0.71	4.8
GG (34)	94.2	39.9	53.2	33.8	1.3	154	21.7	193	30.2	0.81	4.6
<i>P</i> trend	0.17	0.68	0.79	0.77	0.77	0.37	0.61	0.72	0.15	0.67	0.91
<i>MSRA</i> , rs545854											
CC (22)	92.0	39.9	50.7	36.4	1.1	110	17.6	196	33.2	0.56	3.6
CG (32)	97.1	40.7	54.6	32.5	1.3	158	22.5	197	30.5	0.88	5.6
GG (5)	96.7	43.2	53.0	33.6	1.2	136	22.4	189	31.4	0.71	3.5
<i>P</i> trend	0.44	0.66	0.07	0.04	0.07	0.15	0.06	0.97	0.61	0.14	0.11
<i>NRXN3</i> , rs10146997											
AA (41)	94.9	41.6	53.4	33.7	1.3	123	20.3	185	32.2	0.66	4.3

Genotype (n)	Waist (cm)	% Total Fat	% Trunk Fat	% Leg Fat	Trunk/Periphery Fat	Visceral Fat Area (cm ²)	% Visceral Fat Area	Subcutaneous Fat Area (cm ²)	% Subcutaneous Fat Area	Visceral/Subcutaneous Fat	% Liver Fat
AG (15)	97.8	39.8	52.9	33.8	1.2	167	21.0	220	31.1	0.90	5.2
GG (3)	86.2	31.9	48.3	39.2	1.1	153	23.6	182	27.7	0.91	5.1
<i>P</i> trend	0.48	0.11	0.44	0.30	0.57	0.41	0.77	0.27	0.75	0.50	0.80
<i>TFAP2B</i> , rs987237											
AA (31)	97.0	41.6	54.0	33.3	1.3	130	21.5	194	31.6	0.70	5.0
AG (27)	92.5	39.2	51.4	35.4	1.2	134	19.2	200	32.4	0.74	4.3
GG (1)	112.1	48.5	65.3	19.6	2.1	463	35.7	137	11.1	2.11	3.3
<i>P</i> trend	0.26	0.22	0.03	0.01	0.02	0.0001	0.06	0.57	0.07	0.04	0.74

* Mean of regional adiposity variables was obtained in analysis of covariance, with adjustment for age and ethnicity (Japanese American or white). MRI variants for percent visceral or subcutaneous fat area over total abdominal area and for percent liver fat were additionally adjusted for DXA total fat mass.