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RARRES2, encoding the novel adipokine chemerin, is a genetic determinant of disproportionate regional body fat distribution: a comparative magnetic resonance imaging study

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Abstract

Visceral fat mass is a strong and independent predictor of obesity-related disorders. To date, little is known about the genetic determinants of regional body fat distribution in humans. As candidates of regional fat distribution, we investigated the fat mass– and obesity-associated gene, the peroxisome proliferator–activated receptor–δ gene, and the retinoic acid receptor responder 2 (*RARRES2*) gene. We studied whether genetic variation within these genes contributes to the development of disproportionate visceral obesity and obesity-related traits, such as insulin resistance and β-cell dysfunction. We genotyped 337 subjects with an increased risk for type 2 diabetes mellitus for tagging single nucleotide polymorphisms (SNPs) in the 3 genes and performed association analyses with anthropometric data and parameters of insulin sensitivity and β-cell function. All subjects underwent an oral glucose tolerance test; a subset was additionally characterized by a hyperinsulinemic-euglycemic clamp. Body fat distribution was assessed by nuclear magnetic resonance imaging. The fat mass– and obesity-associated gene SNP rs8050136 was nominally associated with body mass index (P = .0130), but not with body fat distribution, after appropriate adjustment. Magnetic resonance imaging–quantified visceral fat mass was significantly associated with *RARRES2* SNP rs17173608 and nominally associated with *RARRES2* SNP rs10278590 in nonobese subjects (P = .0002 and P = .0423, respectively), with carriers of the minor alleles displaying lower visceral adipose tissue mass. Besides, the minor allele of SNP rs17173608 was nominally associated with a lower waist-to-hip ratio (P = .0295). In obese subjects, these associations were not detected. No associations were found between the peroxisome proliferator–activated receptor–δ gene and measures of whole-body adiposity and of body fat distribution. All SNPs were associated neither with insulin sensitivity nor with insulin secretion. Common genetic variation within *RARRES2* is associated with increased visceral fat mass in nonobese subjects. In generalized obesity, this genetic effect may be masked by the close association between whole-body obesity and visceral fat mass.

1. Introduction

Obesity is a growing public health problem worldwide. Generalized obesity is frequently associated with metabolic comorbidities, including glucose intolerance, insulin resistance, pancreatic β-cell dysfunction, and type 2 diabetes mellitus [1]. However, an increasing body of evidence supports the importance of body fat distribution in the development of the aforementioned metabolic disorders [2]. Visceral adipose tissue (VAT) mass was identified as a strong and independent predictor of obesity-related disorders [3]. Thus, individuals who are not obese according to body mass index (BMI) but have large VAT depots are at increased risk for adverse metabolic consequences [4].

Although heritability data for abdominal visceral fat are limited, previous studies clearly indicate, in addition to environmental determinants, the existence of genetic factors

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in the development of visceral obesity [5,6]. The genetic determinants of human fat topography that likely differ from those determining fat mass per se [7] may affect modulation of food intake and energy expenditure, lipid metabolism, and adipocyte differentiation [5].

Therefore, the aim of the present study was to test the impact of common genetic variation in the fat mass– and obesity-associated (*FTO*) gene, the peroxisome proliferator–activated receptor–δ (*PPARD*) gene, and the retinoic acid receptor responder 2 (*RARRES2*) gene on regional fat distribution and obesity-related traits, such as insulin resistance and β-cell dysfunction.

The *FTO* gene was recently identified as a major genetic determinant of adult and childhood obesity by genomewide searches [8-10] and is suggested to play an important role in the central nervous regulation of calorie balance [11,12]. The *PPARD* gene promotes lipid metabolism in peripheral tissues [13]. Recently located to a genetic locus associated with obesity [14], *PPARD* was shown to affect lifestyle intervention–induced changes in fat mass [15]. The *RARRES2* gene encodes the novel adipokine chemerin, also known as *tazarotene-induced gene 2*, which was recently reported to play a role in adipogenesis and adipocyte metabolism [16].

2. Subjects and methods

2.1. Subjects

The 337 nondiabetic subjects (subject characteristics shown in Table 1) at an increased risk for type 2 diabetes mellitus (family history of diabetes, history of gestational diabetes, overweight, or impaired glucose tolerance) were recruited from the ongoing Tübingen Family Study for type 2 diabetes mellitus. Relatedness among subjects was less than 1%. All subjects were metabolically characterized by an oral glucose tolerance test (OGTT); a subgroup of 230 subjects was additionally characterized by a hyperinsulinemic-euglycemic clamp. The participants gave informed written consent to the study. The protocol was approved by the Ethics Committee of the University of Tübingen.

Table 1
Subject characteristics of the total population

Sex (male/female)	127/210
IGT/IFG/(IGT + IFG)	44/38/35
Age (y)	45.5 (18-69)
BMI (kg/m^2)	29.6 (19.4-47.0)
WHR	0.890 (0.608-1.125)
TAT (% body weight)	30.2 (6.7-51.5)
VAT (% body weight)	3.3 (0.4-9.3)
NVAT (% body weight)	26.9 (5.7-47.3)
Fasting glucose (mmol/L)	5.21 (4.16-6.94)
Glucose 120-min OGTT (mmol/L)	6.86 (4.00-11.06)
Fasting insulin (pmol/L)	61.3 (17.0-246.0)
Insulin 30-min OGTT (pmol/L)	517.0 (68.0-2309.0)

Data are presented as means (range). IGT indicates impaired glucose tolerance; IFG, impaired fasting glucose.

2.2. Genotyping of the study population

Recent genomewide association studies revealed the *FTO* gene as a susceptibility locus for both obesity and type 2 diabetes mellitus. rs9939609 and rs8050136 in intron 1 of the *FTO* gene were found to be the 2 most significantly associated single nucleotide polymorphisms (SNPs) [8,10]. As these 2 SNPs are in complete linkage disequilibrium (D' = 1.0 and r^2 = 1.0), we genotyped our study population only for rs8050136 C/A. With rs1053049, rs6902123, and rs2267668, 3 *PPARD* SNPs were chosen that were found to determine the change of body composition during lifestyle intervention [15]. rs1053049 T/C is located in the 3′ untranslated region (UTR) of *PPARD*, and rs6902123 T/C and rs2267668 A/G are located in intron 2 of *PPARD*.

Using the publicly available phase II data of the International HapMap Project derived from a population of Utah residents with ancestry from northern and western Europe (release 22, April 2007, http://www.hapmap.org/index.html.en [17]), 3 SNPs in *RARRES2*—rs3735171, rs10278590, and rs17173608—were manually chosen as representative covering 100% of the common genetic variation (minor allele frequency [MAF] $\geq$0.05) of the locus with D' = 1.0 and r^2 greater than or equal to 0.8. rs3735171 T/C is located in the 3′ flanking region of *RARRES2* as well as in the 5′ (UTR) of the functionally undescribed leucine-rich repeat containing 61 gene, rs10278590 A/C, which has recently been renamed in rs4721, in the 3′ UTR of *RARRES2*, and rs17173608 T/G in intron 3 of *RARRES2*. For none of the analyzed SNPs are functional effects known. Given that these SNPs are located within noncoding regions, they probably affect only gene expression and not the function of the gene product.

DNA was isolated from whole blood using a commercial DNA isolation kit (NucleoSpin; Macherey & Nagel, Düren, Germany). The SNPs were genotyped using the TaqMan assay (Applied Biosystems, Foster City, CA). The TaqMan genotyping reaction was amplified on a GeneAmp PCR System 7000 (50°C for 2 minutes, 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute), and fluorescence was detected on an ABI Prism sequence detector (Applied Biosystems). As a quality standard, we randomly included 6 positive and 2 negative (all components excluding DNA) sequenced controls in each TaqMan reader assay. All controls were correctly identified. The overall genotyping success rate was 99.9% (all SNPs: 100%, except for *RARRES2* rs3735171: 99.1%).

2.2.1. OGTT and hyperinsulinemic-euglycemic clamp

Both assays were performed as previously described in detail [18].

2.2.2. Determination of blood parameters

Plasma glucose, insulin, and C-peptide concentrations were measured as described earlier [18].

2.2.3. Body composition and body fat distribution

Body mass index and waist and hip circumferences were measured as described earlier [18]. Body fat depots were quantified using ^{1}H-nuclear magnetic resonance imaging (MRI) as described earlier [19].

2.2.4. Calculations

The area under the curve (AUC) of plasma metabolite concentrations (c) during the OGTT was calculated as 0.5 ($0.5 \cdot c_0 + c_{30} + c_{60} + c_{90} + 0.5 \cdot c_{120}$). First-phase insulin secretion (in picomoles per liter), insulin sensitivity from the OGTT (in arbitrary units), and clamp-derived insulin sensitivity (in arbitrary units) were calculated as reported earlier [18].

2.2.5. Statistical analyses

Data are given as means ± SE. Log-transformation of metabolic variables was performed before simple and multivariate linear regression analyses. In multivariate linear regression models, the trait was chosen as dependent variable; and sex, age, BMI, and genotype were tested as independent variables. Taking into account that 7 SNPs and 5 phenotypes were tested in parallel, a Bonferroni-corrected *P* value less than .0014 was considered statistically significant. The statistical software package JMP 4.0 (SAS Institute, Cary, NC) was used. In the dominant inheritance model, our study was sufficiently powered ($1 - \beta > 0.8$) to detect effect sizes greater than or equal to 0.34 for rs8050136 in *FTO*; greater than or equal to 0.31 for rs1053049, greater than or equal to 0.42 for rs6902123, and greater than or equal to 0.33 for rs2267668 in *PPARD*; and greater than or equal to 0.31 for rs3735171, greater than or equal to 0.31 for rs10278590, and greater than or equal to 0.47 for rs17173608 in *RARRES2* (2-tailed *t* test). Power calculation was performed using G*power software available at http://www.psycho.uni-duesseldorf.de/aap/projects/gpower. Analysis of linkage disequilibrium (*D*', r^2) was performed using the JLIN program provided by the Western Australian Institute for Medical Research (http://www.genepi.org.au/jlin [20]). Hardy-Weinberg equilibrium was tested using χ^2 test.

3. Results

3.1. Characterization and genotyping of a German population at an increased risk for type 2 diabetes mellitus

We genotyped 337 nondiabetic subjects from the southwest of Germany whose clinical characteristics are presented in Table 1. Most (81.4%) of the subjects had a family history of diabetes, that is, at least 1 second-degree relative with type 2 diabetes mellitus. The following tagging SNPs were analyzed: rs1053049, rs6902123, and rs2267668 in *PPARD*; rs8050136 in *FTO*; as well as rs3735171, rs10278590, and rs17173608 in *RARRES2*. All allele frequencies were in Hardy-Weinberg equilibrium (χ^2 test, $P > .05$). The HapMap and observed MAFs were 0.276 and 0.252, respectively (C allele), for rs1053049;

Table 2
Correlations of *PPARD* SNPs rs1053049, rs6902123, and rs2267668 and *FTO* SNP rs8050136 with anthropometric and metabolic traits

SNP	*PPARD* rs1053049			*PPARD* rs6902123			*PPARD* rs2267668			*FTO* rs8050136		
Genotype	TT	XC	*P*	TT	XC	*P*	AA	XG	*P*	CC	XA	*P*
n	184	153	–	284	53	–	223	111	–	98	239	–
Age (y)	45.8 ± 0.8	45.1 ± 1.0	.4	45.4 ± 0.7	45.8 ± 1.7	.9	45.8 ± 0.8	44.7 ± 1.1	.3	44.6 ± 1.1	45.8 ± 0.8	.4
BMI (kg/m^2)	29.4 ± 0.4	29.9 ± 0.4	.5	29.8 ± 0.3	28.6 ± 0.7	.09	29.2 ± 0.3	30.3 ± 0.5	.10	28.6 ± 0.4	30.1 ± 0.3	.0130
WHR	0.884 ± 0.007	0.898 ± 0.007	.2	0.891 ± 0.006	0.889 ± 0.013	.6	0.883 ± 0.006	0.901 ± 0.009	.7	0.892 ± 0.010	0.890 ± 0.006	.8
TAT (% body weight)	30.6 ± 0.7	29.6 ± 0.7	.7	30.4 ± 0.5	28.9 ± 1.1	.17	30.4 ± 0.6	29.7 ± 0.8	.6	28.8 ± 0.9	30.7 ± 0.8	.08
VAT (% body weight)	3.25 ± 0.12	3.32 ± 0.14	.9	3.28 ± 0.10	3.28 ± 0.25	1.0	3.23 ± 0.11	3.33 ± 0.16	.9	3.10 ± 0.17	3.35 ± 0.11	.05
NVAT (% body weight)	27.3 ± 0.7	26.3 ± 0.7	.7	27.1 ± 0.5	25.6 ± 1.1	.11	27.2 ± 0.6	26.3 ± 0.9	.5	25.7 ± 0.9	27.3 ± 0.6	.08

For statistical analysis, data were log-transformed. Age was adjusted for sex. All body fat measures were adjusted for sex and age.

0.075 and 0.086, respectively (C allele), for rs6902123; 0.192 and 0.183, respectively (G allele), for rs2267668; 0.45 and 0.451, respectively (A allele), for rs8050136; 0.245 and 0.238, respectively (C allele), for rs3735171; 0.383 and 0.372, respectively (C allele), for rs10278590; and 0.05 and 0.064, respectively (G allele), for rs17173608. The observed MAF was similar to the MAF published by HapMap.

3.2. Associations between SNPs and anthropometric and metabolic data

As presented in Table 2, the *FTO* SNP rs8050136 was nominally associated with BMI after adjustment for age and sex in the dominant model, with carriers of the minor allele displaying increased values (P = .0130). Carriers of the minor alleles of the *RARRES2* SNPs rs3735171 and rs10278590 showed nominally lower BMI values (P = .0309 and P = .0296, respectively; Table 3). None of the tested SNPs was associated with waist-to-hip ratio (WHR).

A more detailed analysis of body composition by MRI revealed a trend of increased total adipose tissue (TAT), VAT, and non-VAT (NVAT) mass in carriers of the minor allele of *FTO* SNP rs8050136 after adjustment for age and sex in the dominant model (Table 2). Furthermore, we found a significant association between *RARRES2* SNP rs17173608 and VAT and a nominal association between *RARRES2* SNP rs10278590 and VAT after adjustment for age and sex in the dominant model (P = .0011 and P = .0095, respectively; Table 3). To further corroborate the impact of generalized obesity on the latter findings, we stratified the population for BMI in nonobese (BMI <30 kg/m^2) and obese subjects (BMI ≥30 kg/m^2). Nonobese carriers of the minor allele of SNP rs17173608 displayed a nominally reduced WHR (P = .0295, Fig. 1). In agreement with this finding, in nonobese subjects, the minor allele of SNP rs17173608 was significantly associated with a 35% lower VAT (P = .0002), whereas no such association was found in obese subjects (P = .3, Fig. 1). No association was found between SNP rs17173608 and NVAT either in nonobese or in obese subjects (P = .2 and P = .7, respectively; Fig. 1). Furthermore, we analyzed the impact of rs17173608 on VAT in male and female subjects separately. Our results showing nominal associations between rs17173608 and VAT in male (AA vs XC: 4.32% vs 3.41% body weight, P = .0048) as well as in female subjects (AA vs XC: 2.12% vs 1.61% body weight, P = .0095) indicate that this association is not sex specific.

Whereas, in nonobese subjects, the association between SNP rs10278590 and VAT remained, though weaker (AA vs XC: 3.23% vs 2.70% body weight, P = .0423), there was no such association in obese subjects (AA vs XC: 3.76% vs 3.92% body weight, P = .9). We did not find associations between the SNPs in *PPARD* and *FTO* and measures of regional fat distribution after stratification (data not shown).

In a previous study, chemerin plasma levels were associated with triglycerides and blood pressure [21]. Therefore, we performed an exploratory analysis on the association of common genetic variation in *RARRES2* with the aforementioned variables. We found a nominal association of rs3735171 with diastolic blood pressure (P = .0243) but not with systolic blood pressure and triglyceride plasma levels (both Ps ≥ .8) after adjustment for sex, age, and BMI in the dominant model. Minor allele carriers of rs3735171 depicted higher diastolic blood pressure values. rs10278590 and rs17173608 were not associated with triglyceride levels and with systolic and diastolic blood pressure after appropriate adjustment either in the additive or in the dominant model (all Ps ≥ .1).

All 337 subjects were metabolically characterized by OGTT; 230 of them were additionally characterized by hyperinsulinemic-euglycemic clamp. All SNPs were associated neither with parameters of insulin sensitivity, such as insulin sensitivity indices derived from OGTT (all Ps > .2) and clamp (all Ps ≥ .1), nor with insulin secretion data, including the ratio of AUC C-peptide to AUC glucose during OGTT, after appropriate adjustment (all Ps > .1, data not shown).

Separate analysis in the obese and nonobese groups did not reveal an association between any of the analyzed SNPs and indices of insulin sensitivity and insulin secretion (all Ps ≥ .05). Mean value and range of

Table 3
Correlations of *RARRES2* SNP rs3735171, rs10278590, and rs17173608 with anthropometric and metabolic traits

SNP	*RARRES2* rs3735171			*RARRES2* rs10278590			*RARRES2* rs17173608		
Genotype	TT	XC	*P*	AA	XC	*P*	TT	XG	*P*
n	192	142	–	131	206	–	297	40	–
Age (y)	45.4 ± 0.8	45.4 ± 1.0	1.0	45.2 ± 1.0	45.6 ± 0.8	.6	45.4 ± 0.7	45.7 ± 1.7	.7
BMI (kg/m^2)	30.1 ± 0.4	28.9 ± 0.4	.0309	30.3 ± 0.4	29.2 ± 0.4	.0296	29.6 ± 0.3	29.6 ± 0.9	.8
WHR	0.892 ± 0.007	0.886 ± 0.008	.7	0.898 ± 0.008	0.886 ± 0.007	.16	0.893 ± 0.005	0.867 ± 0.016	.07
TAT (% body weight)	30.5 ± 0.6	29.5 ± 0.8	.12	30.9 ± 0.8	29.7 ± 0.6	.11	30.2 ± 0.5	30.0 ± 1.5	.3
VAT (% body weight)	3.29 ± 0.12	3.23 ± 0.14	.8	3.48 ± 0.15	3.16 ± 0.12	.0095	3.36 ± 0.10	2.69 ± 0.24	**.0011**
NVAT (% body weight)	27.3 ± 0.6	26.3 ± 0.8	.08	27.4 ± 0.8	26.5 ± 0.6	.19	26.8 ± 0.5	27.3 ± 1.5	.7

For statistical analysis, data were log-transformed. Age was adjusted for sex. All body fat measures were adjusted for sex and age. Statistically significant differences are shown in boldface.

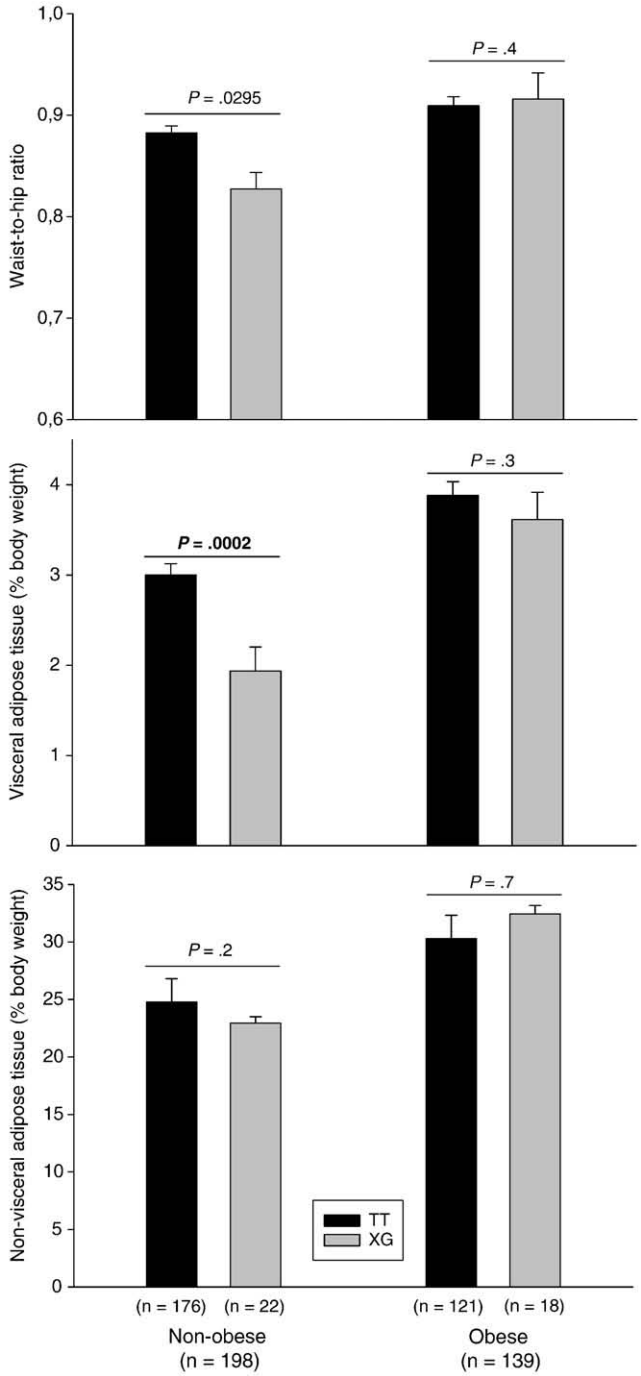

Fig. 1. Association of *RARRES2* SNP rs17173608 with WHR, VAT, and NVAT mass in nonobese vs obese subjects. Unadjusted data from 337 subjects are presented. For statistical reasons, the data were log-transformed, adjusted for sex and age, and analyzed in the dominant model by Student *t* test. *P* values are given above the columns. *Nonobese* was defined as below and *obese* as above BMI of 30.0 kg/m^2.

variation of insulin sensitivity index derived from OGTT and from hyperinsulinemic-euglycemic clamp were 15.0 (2.6-40.4) U and 0.076 (0.022-0.347) U, respectively, in the nonobese group and 10.1 (2.9-33.4) U and 0.047 (0.011-0.116) U, respectively, in the obese group.

4. Discussion

We found associations of the *RARRES2* SNPs rs17173608 and rs10278590 with VAT mass, whereas no associations between these 2 SNPs and NVAT content were detected. These findings suggest that common genetic variation in the *RARRES2* gene locus may specifically contribute to the development of visceral adiposity. In contrast, tagging SNPs in the genes *FTO* and *PPARD*, both known to modulate fat mass, were not associated with body fat distribution. Interestingly, we did not observe an association between *RARRES2* SNPs and visceral adiposity in obese subjects. This finding may be due to the close association between whole-body obesity and visceral fat mass. In generalized obesity, whole-body fat mass appears to be the main determinant of visceral fat mass, whereas this seems not to be the case in lean subjects [22].

Our findings are in line with previous studies showing an association between plasma chemerin concentrations and several aspects of the metabolic syndrome, including elevated BMI, triglyceride levels, and blood pressure [21]. Chemerin is secreted as a poorly active pro-protein of 18-kd prochemerin and undergoes extracellular proteolytic removal of the C-terminal 6 amino acids, resulting in the active 16-kd protein. Chemerin is the ligand of the G-protein–coupled receptor ChemR23, also known as *chemoattractant-like receptor 1*, which is expressed in activated dendritic cells and macrophages [23].

Although initially chemerin was reported to play an important role in the innate and adaptive immunity [24], recent studies point to a crucial role of chemerin in adipocyte metabolism and differentiation. Chemerin and ChemR23 are abundantly expressed in mouse and human adipose tissue [15]. In different obesity animal models, expression of chemerin and its receptor in adipose tissue further increased compared with that in normal-weight controls [15,22]. In accordance with the marked chemerin expression during adipocyte differentiation [22,25], knockdown of chemerin or ChemR23 impaired differentiation of 3T3-L1 preadipocytes into adipocytes. In mature adipocytes, knockdown of chemerin, but not of ChemR23, reduced basal lipolysis by approximately 50% [15]. Thus, chemerin appears to have autocrine and/or paracrine effects on adipocyte function [25,26]. Furthermore, *RARRES2* is a well-known target gene of the retinoic acid receptor α; and a growing body of evidence supports a link between retinoic acid signaling and adipocyte differentiation [27].

Although visceral adiposity is a strong predictor of obesity-related disorders, including insulin resistance [19], we did not detect an association between *RARRES2* SNPs and insulin sensitivity in the nonobese subjects despite the substantial effect on VAT. Potential explanations for the lacking association are the following. First, insulin sensitivity did not show great variation in this nonobese subgroup. Second, VAT-induced insulin resistance may underlie a threshold effect; and the amount of visceral fat mass in most

of our nonobese subjects did not exceed the level required to provoke insulin resistance.

The present study has certain limitations that need to be taken into account. First, further replications in other cohorts phenotyped by MRI or comparable methods are needed to confirm the associations of genetic variation within this locus with visceral adiposity. Second, we performed a relatively large number of statistical tests (7 SNPs and 5 phenotypes), which may increase the risk for a statistical type 1 error. However, even after Bonferroni correction for multiple comparisons (corrected α level: $P < .0014$), the association between SNP rs17173608 and VAT mass remained significant. Furthermore, SNP rs17173608 was nominally associated with WHR, a widely used surrogate measure of visceral adiposity; and with SNP rs10278590, a second *RARRES2* SNP appeared to be associated with visceral adiposity. Although not withstanding Bonferroni correction, these additional associations argue against a by-chance finding.

In conclusion, common genetic variation within the *RARRES2* gene affects visceral fat mass in nonobese subjects. In generalized obesity, this genetic effect may be masked by the close association between whole-body obesity and visceral fat mass.

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References

[1] Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. Epidemiol Rev 2007;29:6-28.

[2] Garg A. Regional adiposity and insulin resistance. J Clin Endocrinol Metab 2004;89:4206-10.

[3] Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000;21:697-738.

[4] Park KS, Rhee BD, Lee KU, et al. Intra-abdominal fat is associated with decreased insulin sensitivity in healthy young men. Metabolism 1991;40:600-3.

[5] Bouchard C, Després JP, Mauriège P. Genetic and nongenetic determinants of regional fat distribution. Endocr Rev 1993;14:72-93.

[6] Bouchard C, Rice T, Lemieux S, Després JP, Pérusse L, Rao DC. Major gene for abdominal visceral fat area in the Québec Family Study. Int J Obes Relat Metab Disord 1996;20:420-7.

[7] Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes 2000;49:883-8.

[8] Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889-94.

[9] Dina C, Meyre D, Gallina S, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 2007;39:724-6.

[10] Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341-5.

[11] Tschritter O, Preissl H, Yokoyama Y, Machicao F, Häring HU, Fritsche A. Variation in the FTO gene locus is associated with cerebrocortical insulin resistance in humans. Diabetologia 2007;50:2602-3.

[12] Fredriksson R, Hägglund M, Olszewski PK, et al. The obesity gene, FTO, is of ancient origin, upregulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain. Endocrinology 2008;149:2062-71.

[13] Keller H, Dreyer C, Medin J, Mahfoudi A, Ozato K, Wahli W. Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator–activated receptor–retinoid X receptor heterodimers. Proc Natl Acad Sci U S A 1993;90:2160-4.

[14] Wuschke S, Dahm S, Schmidt C, Joost HG, Al-Hasani H. A meta-analysis of quantitative trait loci associated with body weight and adiposity in mice. Int J Obes (Lond) 2007;31:829-41.

[15] Thamer C, Machann J, Stefan N, et al. Variations in PPARD determine the change in body composition during lifestyle intervention: a whole-body magnetic resonance study. J Clin Endocrinol Metab 2008;93:1497-500.

[16] Goralski KB, McCarthy TC, Hanniman EA, et al. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem 2007;282:28175-88.

[17] The International HapMap Project. Nature 2003;426:789-96.

[18] Stefan N, Machicao F, Staiger H, et al. Polymorphisms in the gene encoding adiponectin receptor 1 are associated with insulin resistance and high liver fat. Diabetologia 2005;48:2282-91.

[19] Thamer C, Machann J, Stefan N, et al. High visceral fat mass and high liver fat are associated with resistance to lifestyle intervention. Obesity (Silver Spring) 2007;15:531-8.

[20] Carter KW, McCaskie PA, Palmer LJ. JLIN: a java based linkage disequilibrium plotter. BMC Bioinformatics 2006;7:60.

[21] Bozaoglu K, Bolton K, McMillan J, et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007;148:4687-94.

[22] Seidell JC, Oosterlee A, Deurenberg P, Hautvast JG, Ruijs JH. Abdominal fat depots measured with computed tomography: effects of degree of obesity, sex, and age. Eur J Clin Nutr 1988;42:805-15.

[23] Meder W, Wendland M, Busmann A, et al. Characterization of human circulating TIG2 as a ligand for the orphan receptor ChemR23. FEBS Lett 2003;555:495-9.

[24] Parolini S, Santoro A, Marcenaro E, et al. The role of chemerin in the colocalization of NK and dendritic cell subsets into inflamed tissues. Blood 2007;109:3625-32.

[25] Roh SG, Song SH, Choi KC, et al. Chemerin—a new adipokine that modulates adipogenesis via its own receptor. Biochem Biophys Res Commun 2007;362:1013-8.

[26] Takahashi M, Takahashi Y, Takahashi K, et al. Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. FEBS Lett 2008;582:573-8.

[27] Safonova I, Darimont C, Amri EZ, et al. Retinoids are positive effectors of adipose cell differentiation. Mol Cell Endocrinol 1994;104:201-11.