FTO Genotype and 2-Year Change in Body Composition and Fat Distribution in Response to Weight-Loss Diets: The POUNDS LOST Trial

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FTO Genotype and 2-Year Change in Body Composition and Fat Distribution in Response to Weight-Loss Diets

The POUNDS LOST Trial

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Recent evidence suggests that the fat mass and obesity-associated gene (FTO) genotype may interact with dietary intakes in relation to adiposity. We tested the effect of FTO variant on weight loss in response to 2-year diet interventions. FTO rs1558902 was genotyped in 742 obese adults who were randomly assigned to one of four diets differing in the proportions of fat, protein, and carbohydrate. Body composition and fat distribution were measured by dual-energy X-ray absorptiometry and computed tomography. We found significant modification effects for intervention varying in dietary protein on 2-year changes in fat-free mass, whole body total percentage of fat mass, total adipose tissue mass, visceral adipose tissue mass, and superficial adipose tissue mass (for all interactions, P < 0.05). Carriers of the risk allele had a greater reduction in weight, body composition, and fat distribution in response to a high-protein diet, whereas an opposite genetic effect was observed on changes in fat distribution in response to a low-protein diet. Likewise, significant interaction patterns also were observed at 6 months. Our data suggest that a high-protein diet may be beneficial for weight loss and improvement of body composition and fat distribution in individuals with the risk allele of the FTO variant rs1558902. Diabetes 61:3005–3011, 2012

The prevalence of overweight and obesity has increased substantially in the U.S. and worldwide, and the health burden of obesity-related complications has grown accordingly (1–3). Obesity is primarily determined by both genetic and lifestyle factors, including diet, as well as their interactions (4). In the past few years, genome-wide association studies (GWASs) have identified a group of genetic loci associated with BMI and obesity risk (5–7). Among them, the fat mass and obesity-associated gene (FTO) locus shows the strongest effect (5,8). Accumulating evidence has suggested that this locus is involved in the hypothalamic regulation of appetite and dietary energy intake (9,10).

RESEARCH DESIGN AND METHODS

Study population. The POUNDS LOST Trial was conducted from October 2004 through December 2007 at two sites as follows: Harvard School of Public Health and Brigham & Women’s Hospital in Boston, Massachusetts; and the Pennington Biomedical Research Center of Louisiana State University System, Baton Rouge, Louisiana. The design and sample collection have been described previously in detail (22). In brief, the study population was composed of 811 overweight or obese (BMI ranged from 25 to 40 kg/m2) participants aged 30–70 years. Major criteria for exclusion were the presence of diabetes or unstable cardiovascular disease, the use of medications that affect body weight, and insufficient motivation as assessed by interview and questionnaire. Among the 742 participants who were genotyped successfully, 61% were women, 80% were white, 15% were black, 3% were Hispanic, and 2% were Asian or other ethnic groups by self-report. The participants were assigned randomly to one of four diets constituting a two-by-two factorial design; the target percentages of energy derived from fat, protein, and carbohydrate in the four diets were 20, 15, and 65%; 20, 25, and 55%; 40, 15, and 45%; and 40, 25, and 35%. After 2 years, 645 participants (80% of total population) completed the trial. The study was approved by the human subjects committee at each institution and by a data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute. All participants provided written informed consent.

Measurements. In the morning before breakfast, body weight and waist circumference (WC) were measured on 2 days at baseline: 6, 12, and 18 months; and 2 years. BMI was calculated as weight by height squared (kg/m2). A dual-energy X-ray absorptiometry (DEXA) scan was performed on 50% of a random sample from the total study participants (n = 424), including 242 (57.1%) women, using a Hologic QDR 4500A (Waltham, MA) (23). Total fat mass (kg), total fat-free mass (FFM; kg), whole body total percentage of fat mass (FM%) and percentage of trunk fat were obtained once at baseline, 6 months, and 2
years. Computed tomography (CT) was used in 50% of a random sample from those participants who had DEXA scans, resulting in a sample of 25% of the total participants (n = 195), including 113 (58.2%) women. Total adipose tissue (TAT) mass, visceral adipose tissue (VAT) mass, deep subcutaneous adipose tissue (DSAT) mass, and superficial adipose tissue (SAT) mass within the abdomen were measured by standard methods (24), once at baseline, 6 months, and 2 years. Because of radiation exposure, premenopausal women would not subject themselves to CT scans. A series of eight single-slice images were obtained every 10 cm from 2 below and 5 above the fourth and fifth lumbar vertebral interspaces. These contiguous cross-sectional images were analyzed, and then the total volume was calculated from the individual slices. In this analysis, we only included data at baseline, 6 months, and 2 years with all the outcomes because the DEXA and CT scans were only performed at these three time points.

Genotyping. DNA was extracted from the buffy coat fraction of centrifuged blood using the QIAmp Blood Kit (Qiagen, Chatsworth, CA). Single nucleotide polymorphism (SNP) rs1558902 was selected because it had emerged as the top variant of FTO locus for BMI and WC in recent obesity-related GWAS (25,26). The SNP was genotyped successfully in 742 of 811 total participants and 603 of 645 participants who completed the trial using the OpenArray SNP Genotyping System (BioTrove, Woburn, MA). Of the 424 participants who received DEXA scans, 391 were genotyped at baseline, and 224 participants who completed the trial were genotyped. Of the 185 participants who received CT scans, 175 were genotyped at baseline and 105 participants who completed the trial were genotyped. The genotype success rate was 99% in available DNA samples. Replicated genotyping at baseline and 105 participants who completed the trial were genotyped. The genotype frequency was signiﬁcantly different among the participants in the four diet groups (Supplementary Table 1). Likewise, no associations between these three time points.

RESULTS

Characteristics of study population. Baseline characteristics of participants according to the FTO rs1558902 genotype are presented in Table 1. The minor allele frequency (MAF; A allele) was 0.402 in the total population. The genotype frequencies were signiﬁcantly different among the sexes and ethnicities. After adjustment for age, sex, and ethnicity, all variables such as weight, BMI, WC, body composition, and fat distribution had no association with genotype at baseline. Baseline characteristics were similar among participants in the four diet groups (Supplementary Table 1). Likewise, no associations between the FTO genotypes and these measures were observed in the white participants (data not shown).

Effects of FTO rs1558902 genotype on weight and waist: overall and two-factorial analysis. After adjustment for age, sex, ethnicity, baseline BMI, and diet groups, no main effects of the FTO rs1558902 genotype on changes in weight or WC were found in any participants at 6 months and 2 years were analyzed using general linear regression models, with adjustment for covariates including age, sex, ethnicity, carbohydrate, the baseline value for the respective outcome, and baseline BMI. We excluded individuals with missing measures at each time point in the analysis. Moreover, to analyze the potential interactions between genotype and diet intervention, an interaction product term of genotype-diet was included in the models. In a secondary analysis, we used linear mixed models, with time as a repeated measurement factor, to test genetic associations with the trajectory of changes in outcomes in the participants who provided measurements at baseline, 6 months, and 2 years in each of four diet groups over the 2-year intervention by including genotype-time interaction terms. Because an additive genetic effect was reported in the original large-scale GWAS in which the SNP was identified (25,26), additive models were analyzed for genotype. All reported P values were two-sided and a P value of 0.05 was considered statistically signiﬁcant. All data were analyzed with SAS version 9.1 (SAS Institute, Inc., Cary, NC).

### Table 1

Baseline characteristics of the study participants according to FTO rs1558902 genotype

| Participants (n) | TT | TA | AA | P* |
|-----------------|----|----|----|----|
| n Age, years    | 742 | 281 | 325 | 136 | 0.575 |
| Female          | 453 | 188 (41.5) | 188 (41.5) | 77 (17.0) | 0.037 |
| Male            | 289 | 93 (32.2) | 137 (47.4) | 59 (20.4) | 2.0001 |
| Race or ethnic group | White | 179 (30.1) | 285 (48.0) | 130 (21.9) | 0.550 |
| Black           | 112 | 84 (75.0) | 25 (22.3) | 3 (2.7) | 0.887 |
| Hispanic or other | 36 | 18 (50.0) | 15 (41.7) | 3 (8.3) | 0.595 |
| Height, m       | 742 | 1.68 ± 0.08 | 1.69 ± 0.09 | 1.69 ± 0.08 | 0.222 |
| Weight, kg      | 742 | 93.4 ± 14.9 | 92.7 ± 16.3 | 94.7 ± 15.1 | 0.050 |
| BMI, kg/m²      | 742 | 32.9 ± 3.8 | 32.8 ± 4.0 | 33.1 ± 3.7 | 0.550 |
| WC, cm          | 742 | 103.0 ± 12.6 | 103.6 ± 13.7 | 105.1 ± 12.3 | 0.522 |
| Body composition | 391 | 150 | 170 | 31 | 0.197 |
| Total fat, kg   | 742 | 34.8 ± 7.7 | 34.8 ± 7.9 | 36.1 ± 8.1 | 0.915 |
| FFM, kg         | 742 | 60.8 ± 13.2 | 60.3 ± 13.3 | 60.0 ± 12.8 | 0.159 |
| FM%,            | 742 | 36.7 ± 7.1 | 36.8 ± 6.7 | 37.8 ± 6.9 | 0.208 |
| Trunk fat%      | 742 | 37.7 ± 6.1 | 37.8 ± 6.1 | 38.8 ± 6.1 | 0.042 |
| Fat distribution | 175 | 57 | 83 | 35 | 0.442 |
| VAT/DSAT        | 151 | 52 | 68 | 31 | 0.981 |
| SAT/TAT         | 151 | 11.0 ± 2.7 | 11.1 ± 2.8 | 11.4 ± 2.5 | 0.693 |
| SAT             | 151 | 16.7 ± 1.1 | 16.6 ± 4.3 | 16.8 ± 3.3 | 0.474 |

Data are n (%) or mean ± SD unless otherwise indicated. *P values were calculated by χ² test for categorical variables and multivariate ANCOVA for continuous variables after adjusting for age, sex, and ethnicity. Boldface P values indicate statistical significance.
months and 2 years (data not shown). We next examined the genetic effects on changes in weight and WC following a two-factorial design: low versus high fat and low versus high protein. We found that the risk allele (A) was significantly associated with a 1.51-kg greater weight loss in the high-protein group ($P = 0.010$), but not in the low-protein group, by the end of intervention (2 years). The changes in weight and WC were less significant at 6 months (Table 2).

In subgroups treated by different proportions of dietary fat, we did not find significant genetic effects on changes in weight and WC (all $P > 0.05$; Supplementary Table 2). Similarly, in the white participants, we found the risk allele was associated with a 1.38-kg greater weight loss in the high-protein group at 2 years ($P = 0.028$), but not in other subgroups (data not shown).

The *FTO* rs1558902 genotype and changes in body composition by diet intervention. Consistent with the observations of change in body weight, we found that the rs1558902 risk allele (A) was associated with greater loss of total fat, FFM, FM%, and percentage of trunk fat at 2 years in the high-protein group, but not in the low-protein group (Table 2). Tests for genotype-diet protein interaction were significant on changes in FFM and FM% (for interactions, $P = 0.034$ and 0.049, respectively) adjusted for age, sex, ethnicity, carbohydrate, baseline BMI, and the baseline value of body composition (Fig. 1). At 6 months, we only observed gene by protein diet interaction on changes in FFM ($P = 0.008$ for interaction; Fig. 1). The risk allele carriers in the high-protein group had greater loss of FFM than noncarriers, but those in the low-protein group had less loss of FFM compared with noncarriers (Table 2).

We did not find significant genetic effect and interactions between the *FTO* variant and dietary fat intake on changes in body composition in total participants (Supplementary Table 2 and Supplementary Fig. 1). The results in the white participants were similar (data not shown).

| Table 2 | The effects of the *FTO* rs1558902 genotype on weight, body composition, and fat distribution response to dietary protein intervention |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | At 6 months | At 24 months |
|         | $\beta^*$  | SE     | $P$ | $\beta^*$  | SE     | $P$ |
| Low protein† |          |        |     |          |        |     |
| Weight, kg | $-0.11$ | 0.46 | $0.807$ | $0.07$ | 0.65 | $0.914$ |
| WC, cm     | $0.02$  | 0.48 | $0.971$ | $-0.31$ | 0.69 | $0.654$ |
| Body composition |
| Total fat, kg | $0.29$  | 0.47 | $0.544$ | $0.73$  | 0.84 | $0.381$ |
| FFM, kg    | $0.54$  | 0.25 | $0.029$ | $0.64$  | 0.45 | $0.150$ |
| FM%        | $-0.01$ | 0.32 | $0.983$ | $0.36$  | 0.48 | $0.455$ |
| Trunk fat % | $0.09$  | 0.43 | $0.840$ | $0.41$  | 0.61 | $0.495$ |
| Fat distribution |
| TAT        | $0.53$  | 0.47 | $0.260$ | $2.11$  | 0.65 | $0.001$ |
| VAT        | $-0.01$ | 0.22 | $0.949$ | $0.35$  | 0.29 | $0.223$ |
| DSAT       | $0.27$  | 0.20 | $0.164$ | $0.31$  | 0.24 | $0.211$ |
| SAT        | $0.61$  | 0.29 | $0.040$ | $1.46$  | 0.42 | $0.0004$ |
| High protein‡ |          |        |     |          |        |     |
| Weight, kg | $-0.33$ | 0.43 | $0.434$ | $-1.51$ | 0.58 | $0.010$ |
| WC, cm     | $0.04$  | 0.46 | $0.933$ | $-0.68$ | 0.62 | $0.270$ |
| Body composition |
| Total fat, kg | $-0.80$ | 0.43 | $0.061$ | $-1.60$ | 0.63 | $0.011$ |
| FFM, kg    | $-0.49$ | 0.23 | $0.031$ | $-0.63$ | 0.30 | $0.035$ |
| FM%        | $-0.46$ | 0.29 | $0.112$ | $-1.13$ | 0.41 | $0.006$ |
| Trunk fat % | $-0.54$ | 0.39 | $0.162$ | $-1.42$ | 0.54 | $0.009$ |
| Fat distribution |
| TAT        | $-0.72$ | 0.32 | $0.024$ | $-1.31$ | 0.55 | $0.017$ |
| VAT        | $-0.43$ | 0.13 | $0.001$ | $-0.64$ | 0.24 | $0.007$ |
| DSAT       | $-0.09$ | 0.12 | $0.425$ | $-0.10$ | 0.20 | $0.625$ |
| SAT        | $-0.24$ | 0.19 | $0.215$ | $-0.58$ | 0.31 | $0.059$ |

Boldface $P$ values indicate statistical significance. †$\beta$ represents change in each trait for each A allele of the *FTO* genotype. Values calculated from the regression models with each trait as the outcome, adjusting for age, sex, ethnicity, carbohydrate, baseline values for respective outcomes, and baseline BMI. ‡Data included from 375, 329, and 301 participants for weight; 375, 328, and 278 participants for WC; 198, 149, and 89 participants for body composition; 80, 57, and 38 participants for TAT and SAT; and 89, 66, and 49 participants for VAT and DSAT in the low-protein group at baseline, 6 months, and 2 years, respectively. ‡Data included from 367, 336, and 302 participants for weight; 367, 334, and 283 participants for WC; 193, 161, and 125 participants for body composition; 71, 56, and 46 participants for TAT and SAT; and 86, 71, and 56 participants for VAT and DSAT in the high-protein group at baseline, 6 months, and 2 years, respectively.
DISCUSSION

In the POUNDS LOST Trial, a 2-year, randomized weight-loss intervention, we found that dietary protein intake significantly modified the effect of an FTO variant on changes in body composition and fat distribution. Carriers of the risk allele (A allele) of the rs1558902 genotype had a greater loss of weight and regional fat in response to a high-protein diet compared with noncarriers, whereas an opposite genetic effect was observed regarding changes in fat distribution in response to a low-protein diet. Our data indicate that the modification effects of dietary treatment were more evident with prolonged intervention. We did not observe significant modification of dietary fat intake on the genotype effects.

The rs1558902 genotype was reported to show the strongest association with obesity in the European (25,26) and other ethnic populations (28), and it has strong linkage disequilibrium with other obesity-associated FTO variants such as the rs9939609 genotype. In this study, the MAF of the polymorphism in all participants was similar to those in the HapMap CEU population (0.45). At baseline, no significant difference was observed in anthropometrics and metabolic estimates, body composition, or fat distribution across genotypes. The lack of association with baseline BMI is probably largely due to the fact that the participants were all overweight or obese, so that the groups had relatively smaller variances in BMI than the general population.

Several cross-sectional studies showed that diets might modify the effect of the FTO variant on obesity, but the data from randomized diet intervention trials are conflicting and limited by small sample size or short term of follow-up (Supplementary Table 3). Two lifestyle intervention studies with follow-up periods of 9 and 12 months did not find significant influence of FTO polymorphisms (rs8050136 and rs9939609) on changes in body weight or fat distribution related to diet among overweight and obese individuals treated by diets with reduced fat and increased fiber or reduced fat and sugar (13,14). In another 10-week, hypo-energetic diet intervention with either low fat or high fat content, the FTO variant had an effect on only changes in resting energy expenditure, insulin release, and sensitivity, not on weight loss (15). Similarly, in the Finnish Diabetes Prevention Study, the FTO variant did not modify weight change by individualized diet intervention with reduced fat and increased fiber during the 4-year follow-up of 255 individuals with impaired glucose tolerance (16). In our study, when macronutrient components of diets were not considered, we found no main effects of the FTO variant on changes in weight and body composition during the intervention.

Grau et al. (15,29) reported that dietary fat/carbohydrate content interacted with some genetic variants including the FTO variant on weight reduction or change in obesity-related phenotypes. In our study, we also found significant gene-diet interactions on changes in body composition and fat distribution. However, our data indicate that it is the dietary protein component, rather than dietary fat, that might drive the observed interactions. In previous studies, high-protein intervention has been found to result in a greater weight loss and abdominal fat mass (30–32). Our results suggest that individuals with a certain genetic
background may benefit more in weight loss by following a high-protein diet. The mechanism of how protein intake interacts with FTO genotype is unclear.

Our data indicate that the genetic effects on certain fat compositions or depots may be more evident than the effects on overall adiposity. Functional studies have shown that the loss or overexpression of FTO in mice led to different changes in fat distribution at different dissected sites (19–21). FTO mRNA expression was depot-specific and was found to differ significantly in subcutaneous fat and in visceral fat (33–35). Epidemiological studies also have shown that FTO variants are significantly associated with distribution of fat depots (13,36,37). Taken together, these data suggest that genetic effects of FTO on the change of fat mass at various sites may be different, and changes in anthropometrics may not adequately reflect the effects of an FTO variant.

The genetic effect in our study seemed to be more evident at 2 years than at 6 months. The results were in line with a recent study by Razquin et al. (18) in which it was found that FTO risk allele carriers had the highest weight reduction after 3 years of intervention with a Mediterranean diet compared with several short-term diet interventions (less than 1 year) in which no influence of an FTO variant on weight loss or change in fat distribution was found (13–15,17). Of note, between 6 months and 2 years of intervention in our trial, the participants regained weight. Therefore, it seems that the genetic variant might affect both the reduction and regain of the adiposity measures. These data suggest that the modification effects of diet treatment on an FTO genotype effect are more likely to be identified in long-term interventions.

Several limitations need to be considered when interpreting our findings. Even though our study is thus far the largest and longest diet intervention weight-loss trial, the relatively small sample size of the subgroups may limit the power to detect very moderate genetic effects or interactions. We did not adjust for multiple testing according to the recommendation by Rothman (38) and Lai et al. (39) because outcomes and the repeated measurements at 6 months and 2 years were highly correlated in our study. Overadjustment for multiple comparisons may increase the type II error and reduce power to detect significant differences. In addition, the majority of the total participants were white, and further studies are needed to determine whether our findings are generalizable to other ethnic groups. Even though the randomized clinical trial is thought to be the best model to test gene-environment interactions, we acknowledge that replication in diverse populations is needed to verify our findings.

In summary, we found that dietary protein intake might modify the FTO variant’s effect on changes in body composition and fat distribution. A high-protein

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**FIG. 2.** Interaction between the FTO rs1558902 genotype and dietary protein intervention on changes in TAT (A), VAT (B), DSAT (C), and SAT (D) at 6 months and 2 years. P values are adjusted for age, sex, ethnicity, carbohydrate, baseline values for respective outcomes, and baseline BMI. Data included 17, 18, and 17 (TT); 30, 35, 35, and 30 (TA); and 10, 13, 13, and 10 (AA) participants in the low-protein group and 18, 22, 22, and 18 (TT); 26, 35, 35, and 26 (TA); and 12, 14, 14, and 12 (AA) in the high-protein group for VAT, TAT, DSAT, and SAT at 6 months (total n = 137); and 12, 15, 15, and 12 (TT); 18, 25, 25, and 18 (TA); and 8, 9, 9, and 8 (AA) participants in the low-protein group and 15, 17, 17, and 15 (TT); 23, 30, 30, and 23 (TA); and 8, 9, 9, and 8 (AA) in the high-protein group for TAT, VAT, DSAT, and SAT at 2 years (total n = 105).
diet may be beneficial for weight loss in individuals with the risk allele of an FTO variant. Further studies are warranted to verify our findings and explore the potential mechanisms.

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FIG. 3. Changes in total fat (A), FFM (B), FM% (C), and percentage of trunk fat (D) in the low-protein and high-protein diet groups according to the FTO rs1558902 genotype from baseline to 6 months and 2 years. P values are adjusted for age, sex, ethnicity, carbohydrate, baseline values for respective outcomes, and baseline BMI. Data included 198, 149, and 99 in the low-protein group and 193, 161, and 125 in the high-protein group for body composition at baseline, 6 months and 2 years, respectively. (A high-quality color representation of this figure is available in the online issue.)

FIG. 4. Changes in TAT (A), VAT (B), DSAT (C), and SAT (D) in the low-protein and high-protein diet groups according to the FTO rs1558902 genotype from baseline to 6 months and 2 years. P values are adjusted for age, sex, ethnicity, carbohydrate, baseline values for respective outcomes, and baseline BMI. Data included values at baseline and at 6 months and 2 years for 80, 57, and 38 participants, respectively, for TAT and SAT and 89, 66, and 49 participants, respectively, for VAT and DSAT in the low-protein group; and 71, 56, and 46 participants, respectively, for TAT and SAT and 86, 71, and 56 participants, respectively, for VAT and DSAT in the high-protein group. (A high-quality color representation of this figure is available in the online issue.)
Lappalainen TJ, Tolppanen AM, Kolehmainen M, et al; Finnish Diabetes Prevention Study Group. The common variant in the FTO gene did not modify the effect of lifestyle changes on body weight: the Finnish Diabetes Prevention Study. Obesity (Silver Spring) 2009;17:832–836

Reinehr T, Hinney A, Nothnagel ME, Hebebrand J. Aggravating effect of INSIG2 and FTO on weight reduction in a one-year lifestyle intervention. Arch Dis Child 2009;94:955–967

Razquin C, Martinez JA, Martinez-Gonzalez MA, Bes-Rastrollo M, Fernandez-Crehuet J, Martí A. A 3-year intervention with a Mediterranean diet modified the association between the rs9939600 variant in FTO and body weight changes. Int J Obes (Lond) 2010;34:266–272

Fischer J, Koch L, Emmenegger U, et al. Inactivation of the Pto gene protects from obesity. Nature 2009;458:804–808

Church C, Lee S, Bagg EA, et al. A mouse model for the metabolic effects of the human fat mass and obesity associated FTO gene. PLoS Genet 2009;5:e1000590

Church C, Moir L, McMurry F, et al. Overexpression of Pto leads to increased food intake and results in obesity. Nat Genet 2010;42:1086–1092

Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–873

Lovejo JC, Smith SR, Rood JC. Comparison of regional fat distribution and health risk factors in middle-aged white and African American women: The Healthy Transitions Study. Obes Res 2001;9:10–16

Kivist H, Chowdhury B, Grangier U, Tylén U, Sjöström L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. Am J Clin Nutr 1988;48:1351–1361

Heard-Costa NL, Zillikens MC, Mondla KL, et al. NRNX3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet 2009;5:e1000539

Speliotes EK, Willer CJ, Berndt SI, et al; MAGIC, Procardis Consortium. Association analyses of 79,706 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010;42:937–948

Qi Q, Bray GA, Smith SR, Hu FB, Sacks FM, Qi L. Insulin receptor substrate-1 gene variation modifies insulation resistance response to weight-loss diets in a 2-year randomized trial: the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial. Circulation 2011;124:565–571

Hotta K, Nakata Y, Matsuo T, et al. Variations in the FTO gene are associated with severe obesity in the Japanese. J Hum Genet 2008;53:546–553

Grau K, Cauchi S, Holst C, et al. TCF7L2 rs7903146-macronutrient interaction in obese individuals’ responses to a 10-wk randomized hypo-energetic diet. Am J Clin Nutr 2010;91:472–479

Larsen TM, Daliskov SM, van Baak M, et al; Diet, Obesity, and Genes (Diogenes) Project. Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med 2010;363:2102–2113

Grützke O, Bastiaans K, Keukeleire D, Van Houtte B, Bastiaans K, Keukeleire D, et al. High-protein diets decrease total and abdominal fat and improve CVD risk profile in overweight and obese men and women with elevated triacylglycerol. Nutr Metab Cardiovasc Dis 2009;19:548–554

Te Morenga LA, Levers MT, Williams SM, Brown RC, Mann J. Comparison of high protein and high fiber weight-loss diets in women with risk factors for the metabolic syndrome: a randomized trial. Nutr J 2011;10:46

Kloting N, Schlentitz D, Ruschke K, et al. Inverse relationship between obesity and FTO gene expression in visceral adipose tissue in humans. Diabetologia 2008;51:641–647

Zabena C, González-Sánchez JL, Martínez-Larrad MT, et al. The FTO obesity gene. Genotyping and gene expression analysis in morbidly obese patients. Obes Surg 2009;19:87–95

Terra X, Auguet T, Forras JA, et al. Anti-inflammatory profile of FTO gene expression in adipose tissues from morbidly obese women. Cell Physiol Biochem 2010;26:1041–1050

Hotta K, Nakamura M, Nakamura T, et al. Polymorphisms in NRNX3, TFFAP2B, MSRA, LYPPL1, FTO and MC4R and their effect on visceral fat area in the Japanese population. J Hum Genet 2010;55:738–742

López-Bermejo A, Petry CJ, Díaz M, et al. The association between the FTO gene and fat mass in humans develops by the postnatal age of two weeks. J Clin Endocrinol Metab 2008;93:1501–1505

Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology 1990;1:43–46

Lai CQ, Demissie S, Cupples LA, et al. Influence of the APOA5 locus on plasma triglyceride, lipoprotein subclasses, and CVD risk in the Framingham Heart Study. J Lipid Res 2004;45:2096–2105