Gene Variants of *TCF7L2* Influence Weight Loss and Body Composition During Lifestyle Intervention in a Population at Risk for Type 2 Diabetes

Axel Haupt,[1] Claus Thamer,[1] Martin Heni,[1] Caroline Ketterer,[1] Jürgen Machann,[2] Fritz Schick,[2] Fausto Machicao,[1] Norbert Stefan,[1] Claus D. Claussen,[2] Hans-Ulrich Häring,[1] Andreas Fritsche,[1,3] and Harald Staiger[1]

OBJECTIVE—The impact of the diabetes risk gene transcription factor 7-like 2 (*TCF7L2*) on body weight is unclear. As *TCF7L2* is expressed in adipose tissue and involved in Wnt-dependent regulation of adipogenesis, we studied the impact of *TCF7L2* variants on body composition and weight loss during lifestyle intervention.

RESEARCH DESIGN AND METHODS—We genotyped 309 German subjects at increased risk for type 2 diabetes for single nucleotide polymorphisms (SNPs) rs7903146, rs12255372, rs11196205, and rs7895340 in *TCF7L2* and performed oral glucose tolerance tests before and after a 9-month lifestyle intervention. Fat distribution was quantified using whole-body magnetic resonance imaging/spectroscopy in a subgroup of 210 subjects.

RESULTS—After adjustment for confounding variables, we observed a negative impact of the type 2 diabetes allele of SNP rs7903146 on change in BMI ($P = 0.0034$) and on changes in nonvisceral ($P = 0.0032$) and visceral fat ($P = 0.0165$) during lifestyle intervention. An association of rs7903146 with lifestyle intervention-induced changes in insulin secretion, glucose concentrations, liver fat, or insulin sensitivity were not detected (all $P > 0.2$). Essentially the same results were obtained with SNP rs1255372. In contrast, we found no effects of SNPs rs11196205 and rs7895340 on change in BMI (all $P \geq 0.5$).

CONCLUSIONS—Our data reveal that diabetes-associated alleles of *TCF7L2* are associated with less weight loss in response to lifestyle intervention. Thus, diabetes-associated *TCF7L2* gene variation predicts the success of lifestyle intervention in terms of weight loss and determines individual susceptibility toward environmental factors. ***Diabetes*** **59:747–750, 2010**

From the [1]Department of Internal Medicine, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, Eberhard-Karls-University Tübingen, Tübingen, Germany; the [2]Section on Experimental Radiology, Department of Diagnostic Radiology, Eberhard-Karls-University Tübingen, Tübingen, Germany; and the [3]Section on Nutritional and Preventive Medicine, Department of Internal Medicine, Eberhard-Karls-University Tübingen, Tübingen, Germany.

Corresponding author: Hans-Ulrich Häring, hans-ulrich.haering@med.uni-tuebingen.de.

Received 20 July 2009 and accepted 10 December 2009. Published ahead of print at http://diabetes.diabetesjournals.org on 22 December 2009. DOI: 10.2337/db09-1050.

Variation in the transcription factor 7-like two (*TCF7L2*) gene strongly determines the risk of type 2 diabetes (1) mainly via what is believed to be its effects on β-cell function, and the insulin secretion deficit of carriers of the diabetes risk alleles (2) may be explained at least in part by incretin resistance (3,4).

The association of *TCF7L2* with weight-related traits and body fat in humans is unclear. Conflicting data are reported on the issue of whether there is an influence of *TCF7L2* variants on insulin resistance (5–7) or liver fat (8), and a modulation of BMI (9,10) and obesity was postulated (11). Helgason et al. (12) defined two haplotypes, $HapB_{type\ 2\ diabetes}$ (rs7903146 efficiently tags HapB in all HapMap groups), which is mainly associated with type 2 diabetes, and HapA (rs7924080 efficiently tags HapA in all HapMap groups), which shows a suggestive association with BMI and altered concentrations of hunger-satiety hormones.

A role of *TCF7L2* in adipocyte differentiation is hypothesized for the following reasons: *1*) *TCF7L2* is expressed in subcutaneous and visceral adipose tissue (11,13,14), and a decrease in *TCF7L2* expression in adipose tissue could be demonstrated during caloric restriction (11); *2*) *TCF7L2* is part of the Wnt signaling cascade, and Wnt signaling inhibits adipogenesis (15–17); and *3*) a polymorphism in the Wnt receptor LRP6 is associated with obesity, the metabolic syndrome, and bone loss (18).

In this study, we investigated whether *TCF7L2* variants, first, are associated with body fat composition and ectopic lipid storage in our cross-sectional setting or, second, interfere with changes in body composition or weight loss during lifestyle intervention. To this end, we used a whole-body magnetic resonance imaging (MRI) approach enabling precise quantification of body fat stores and magnetic resonance spectroscopy (MRS) to measure ectopic fat deposition in the liver. In our analyses, we focused on single nucleotide polymorphisms (SNPs) rs7903146 and rs1255372, which have yielded the best association with type 2 diabetes across multiple Caucasian populations and tag haplotype $HapB_{type\ 2\ diabetes}$ (1–3). In addition, we also investigated SNPs rs1196205 and rs7895340, which were available in our cohort, are in near-complete linkage with SNP rs7924080 (both $r^2 \geq 0.89$, HapMap data), and therefore efficiently tag haplotype HapA (12).

RESEARCH DESIGN AND METHODS

We studied 309 nondiabetic German Caucasian subjects who participated in the ongoing Tuebingen Lifestyle Intervention Program (TULIP) (19). The subjects were at increased risk for type 2 diabetes (20). Most of these subjects (~70%) had a family history of diabetes. About 13% of the study subjects were

TABLE 1
Anthropometric and metabolic parameters at baseline and changes during lifestyle intervention

	Mean ± SD	Range	$\Delta = T_{\text{follow up}} - T_{\text{baseline}}$	Mean ± SD	*P*
Age (years)	46 ± 11	18–69			
BMI (kg/m^2)	30.1 ± 5.6	19.4–51.0	ΔBMI	−0.9 ± 1.5	<0.0001
Total body fat (%)	33.0 ± 8.6	9.8–58.3	ΔTotal body fat	−1.1 ± 4.5	<0.0001
Fasting glucose (mmol/l)	5.3 ± 0.5	4.1–6.5	ΔFasting glucose	−0.1 ± 0.5	0.0011
$\text{Glucose}_{120\text{-min}}$ (mmol/l)	7.0 ± 1.6	3.6–11.1	$\Delta\text{Glucose}_{120\text{-min}}$	−0.3 ± 1.6	<0.0001
$\text{AUC}_{\text{C-Peptide}}/\text{AUC}_{\text{Glucose}}$ ($\times 10^{-9}$)	1,217 ± 660	60–4,385	$\Delta\text{AUC}_{\text{C-Peptide}}/\text{AUC}_{\text{Glucose}}$	−0.4 ± 74	0.9
Insulin sensitivity, OGTT (AU)	12.8 ± 6.9	2.6–32.5	ΔInsulin sensitivity	1.8 ± 6.2	<0.0001
Nonvisceral fat (kg)*	23.2 ± 10	3.4–60.5	ΔNonvisceral fat	−2.0 ± 3.4	<0.0001
Visceral fat (kg)*	3.0 ± 1.8	0.3–10.1	ΔVisceral fat	−0.4 ± 0.6	<0.0001
Liver fat content (% of water signal)*	6.6 ± 8.3	0.2–44.7	ΔLiver fat content	−2.1 ± 5.9	<0.0001

n (female/male) = 194/115. Changes during lifestyle intervention were statistically analyzed by MANOVA. *MRI/MRS subcohort.

related to each other. Oral glucose tolerance tests (OGTTs) revealed that 60% of the nondiabetic participants had normal glucose tolerance, 13% had impaired fasting glycemia, 14% had impaired glucose tolerance, and 13% had both impaired fasting glycemia and impaired glucose tolerance.

OGTT. After an overnight fast, subjects ingested a solution containing 75-g glucose at 08:00 h. Plasma glucose, insulin, and C-peptide concentrations were determined at 0, 30, 60, 90, and 120 min thereafter.

Body composition. Total body fat was measured by bioelectrical impedance (BIA-101; RJL Systems, Detroit, MI). In a subgroup of 210 subjects, an exact quantification of fat distribution was performed by MRI and MRS. Magnetic resonance examinations were performed on a 1.5-T whole-body imager (Magnetom Sonata; Siemens Medical Solutions, Erlangen, Germany). A whole-body imaging protocol was applied for recording a set of 90–120 parallel transverse slices. Slice thickness was 10 mm for the entire body. T1-weighted contrast was applied, allowing semiautomatic quantitative assessment of fatty tissue and other tissue types in each cross-section. MRI-derived visceral, nonvisceral, and total fat mass are given in kilograms. Hepatic fat content was determined by localized stimulated echo acquisition mode (STEAM) ^{1}H-magnetic resonance spectroscopy (repetition time [TR] = 4 s, echo time [TE] = 10 ms; 32 scans). The lipid content was quantitatively assessed by analyzing the signal integral using the liver water signal integral as an internal reference. MRS-derived hepatic fat is given in percent of water signal (21).

Lifestyle intervention. TULIP consists of exercise and dietary intervention for 2 years, which was adopted from the intervention used in the Finnish Diabetes Prevention Study (DPS) (10) and was previously reported (19). Since this is an ongoing project and most data are available for the baseline and 9-month visit, we analyzed these data in the present study. The participants aimed at a weight loss of at least 5%, a reduction of caloric intake from fat to <30% and an increase of fiber intake to at least 15 g/1,000 kcal. Individuals were asked to perform at least 3 h of moderate exercise per week, which was monitored using a heart rate monitor (Polar, Büttelborn, Germany). All individuals had up to 10 sessions with a dietitian during the 9 months. Informed written consent was obtained from all participants, and the local ethics committee approved the protocol.

Genotyping. DNA from whole blood was isolated using a commercial DNA isolation kit (NucleoSpin; Macherey & Nagel, Düren, Germany). Genotyping was performed using the TaqMan assay (Applied Biosystems, Forster City, CA). The TaqMan genotyping reaction was amplified on a GeneAmp PCR system 7000, and fluorescence was detected on an ABI PRISM 7000 sequence detector (Applied Biosystems). The genotyping success rates were 99.9% for SNP rs7903146, 99.6% for SNP rs12255372, 99.1% for rs11196205, and 98.9% for rs7895340. The genotypes were verified in 50 randomly selected subjects by bidirectional sequencing, and both methods yielded 100% identical results.

Analytical procedures. Plasma insulin and C-peptide levels were determined with a commercial chemiluminescence system (ADVIA Centaur; Siemens Medical Solutions, Fernwald, Germany). Blood glucose was measured using a bedside glucose analyzer and the glucose oxidase method. (Yellow Springs Instruments, Yellow Springs, OH).

Calculations. The area under the curve (AUC) of glucose and C-peptide during the OGTT was calculated according to the trapezoid method. Insulin sensitivity during the OGTT was estimated according to the formula: 10,000/(fasting glucose × fasting insulin × mean glucose [OGTT] × mean insulin [OGTT])$^{1/2}$.

Statistical analyses. Unless otherwise stated, data are given as means ± SD. Data that were not normally distributed were logarithmically transformed prior to statistical analysis. Hardy-Weinberg equilibrium was tested using the χ^2 test. Differences in parameters between genotypes were tested using multivariate linear regression analysis. Differences with a *P* value <0.05 were considered statistically significant. The JMP 7.0 (SAS Institute, Cary, NC) statistical software package was used.

Power calculation. The study was sufficiently powered ($1 - \beta = 0.93$) to detect effect sizes as small as SD/5 in the overall cohort for change in BMI.

RESULTS

The observed minor allele frequency for SNP rs7903146 was 34%, for rs12255372 it was 29%, for rs11196205 it was 48%, and for rs7895340 it was 46%. All SNPs were in Hardy-Weinberg equilibrium ($P \geq 0.4$).

All data were adjusted for sex and age. Glucose concentrations, insulin secretion, and insulin sensitivity derived from the OGTT were additionally adjusted for BMI. The effect of the lifestyle intervention on glucose metabolism, body composition, and weight loss was reported previously (19). Subject characteristics and effect of lifestyle intervention are presented in Table 1.

In the cross-sectional setting, we found no association of the type 2 diabetes risk SNP rs7903146 with insulin sensitivity, BMI, bioimpedance-derived total body fat, visceral fat mass, nonvisceral fat mass, or liver fat (all $P \geq 0.2$) (Table 2). However, we observed a trend for lower insulin secretion as measured by $\text{AUC}_{\text{C-Peptide}}/\text{AUC}_{\text{Glucose}}$ ($P \leq 0.07$) and higher 120-min glucose ($P \leq 0.1$) in type 2 diabetes risk allele carriers (Table 2).

During lifestyle intervention, the risk allele carriers displayed lower reduction in BMI ($P \leq 0.0108$) and total body fat ($P_{\text{dom}} = 0.0155$; $P_{\text{add}} = 0.07$) (Table 2). SNP rs7903146 explained 2.6% of the variation in the intervention-induced change of BMI. The variant was not associated with changes in fasting or 120-min glucose, insulin sensitivity, liver fat, or insulin secretion (all $P \geq 0.09$). Because of the known effect of the variant on insulin secretion, we additionally adjusted the effect on change in BMI for insulin secretion and 120-min glucose. This however did not alter the results.

In the MRI/MRS cohort, we observed in the risk allele carriers a lower reduction in nonvisceral ($P_{\text{dom}} = 0.0022$; $P_{\text{add}} = 0.06$) and visceral fat mass ($P_{\text{dom}} = 0.0165$; $P_{\text{add}} = 0.06$) (Table 2). As adjustment for sex and age does not completely account for sex- and age-specific interaction effects of rs7903146 on body composition and weight loss, we performed separate analyses for male and female and old and young (separated by the median) study participants (supplemental Tables 1 and 2, available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db09-1050/DC1). After stratification for sex, most of the associations observed in the overall cohort were also seen in the subgroups, and no clear sex effects

TABLE 2
Associations of *TCF7L2* SNP rs7903146 with anthropometric and metabolic parameters in the cross-sectional setting and with changes in these parameters during lifestyle intervention by genotype

	CC	XT	*P*1	*P*2		CC	XT	*P*1	*P*2
n (female/male)	148 (95/53)	161 (99/62)	—						
Age (years)	46 ± 10	47 ± 12	—						
BMI (kg/m^2)	30.3 ± 5.5	30.0 ± 5.8	0.5	0.7	ΔBMI	−1.2 ± 1.6	−0.7 ± 1.5	**0.0034**	**0.0108**
Total body fat (%)	33.7 ± 8.5	32.5 ± 8.7	0.3	0.3	ΔTotal body fat	−1.7 ± 4.5	−0.5 ± 4.3	**0.0155**	0.07
Fasting glucose (mmol/l)	5.3 ± 0.5	5.3 ± 0.5	0.95	0.9	ΔFasting glucose	−0.1 ± 0.4	0.0 ± 0.4	0.2	0.1
$Glucose_{120\text{-}min}$ (mmol/l)	6.8 ± 1.5	7.2 ± 1.7	0.05	0.1	$\Delta Glucose_{120\text{-}min}$	−0.2 ± 1.6	−0.4 ± 1.5	0.4	0.8
$AUC_{C\text{-}Peptide}/AUC_{Glucose}$ ($\times 10^{-9}$)	317 ± 96	295 ± 88	0.06	0.07	$\Delta AUC_{C\text{-}Peptide}/AUC_{Glucose}$	−2.6 ± 78	1.5 ± 70	0.3	0.8
Insulin sensitivity, OGTT (AU)	12.5 ± 7.0	13.0 ± 6.8	0.4	0.6	ΔInsulin sensitivity	2.2 ± 6.0	1.5 ± 6.4	0.6	0.5
Nonvisceral fat (kg)*	23.5 ± 9.5	22.8 ± 10.3	0.5	0.8	ΔNonvisceral fat	−2.7 ± 3.6	−1.3 ± 2.9	**0.0022**	0.06
Visceral fat (kg)*	3.0 ± 1.8	3.0 ± 1.9	0.2	0.3	ΔVisceral fat	−0.5 ± 0.6	−0.3 ± 0.6	**0.0165**	0.06
Liver fat content (% of water signal)*	7.6 ± 9.3	5.7 ± 7.0	0.3	0.2	ΔLiver fat content	−2.7 ± 5.8	−1.5 ± 5.9	0.09	0.2

Data are means ± SD. BMI and total body fat were adjusted for sex and age. Glucose concentration, insulin secretion, and insulin sensitivity were additionally adjusted for BMI. $\Delta = T_{follow\ up} - T_{baseline}$. The change in the parameters was additionally adjusted for baseline values. The change in glucose concentration, insulin secretion, and insulin sensitivity was adjusted for the change in BMI. Data were statistically analyzed by multivariate linear regression analysis in the dominant inheritance model, *P*1, and the additive inheritance model, *P*2. Data in bold represent statistical significance. *MRI/MRS subcohort.

could be detected. After stratification for age, however, the associations of the overall cohort were only reflected in the young subgroup.

To minimize the chance of statistical type 1 errors, we additionally analyzed SNP rs12255372, which is in incomplete linkage disequilibrium with rs7903146 ($r^2 = 0.77$, HapMap data). Essentially the same results were obtained with rs12255372 (supplemental Table 3).

In contrast, SNPs rs11196205 and rs7895340 (tagging haplotype HapA) were not associated with body composition cross-sectionally or with weight loss during lifestyle intervention (all $P > 0.5$) (supplemental Tables 4 and 5).

DISCUSSION

In the present study, we found in a population at risk for type 2 diabetes that risk variants for type 2 diabetes of the *TCF7L2* gene (rs7903146, rs12255372) influence lifestyle intervention-induced changes in BMI, total fat, and nonvisceral and visceral fat, while changes in insulin secretion, insulin sensitivity, or blood glucose are unaffected. Like our cross-sectional setting, most cross-sectional studies found no reliable association of variants in *TCF7L2* gene with BMI (1,3,22). Nevertheless, Helgason et al. (12) observed a moderately leaner phenotype in carriers of the haplotype $HapB_{type\ 2\ diabetes}$ (0.44% lower BMI per copy). The finding of a leaner phenotype is confirmed in the cross-sectional analyses of the Diabetes Prevention Program (DPP) and the DPS (9,10). The authors of the DPP concluded that their finding is unexpected and possibly artificial (9). Subjects with lower insulin secretion, like the *TCF7L2* risk allele carriers, had a higher risk to develop diabetes even though they were leaner. Therefore, there may be a bias in the study population when enrolling only subjects at risk for type 2 diabetes (9). Although the HapA haplotype is reported to associate with BMI and altered concentrations of hunger-satiety hormones (12), the HapA-tagging SNPs tested in our cohort were not associated with weight loss in the longitudinal setting.

In the DPS as well as in the DPP, it was shown that the diabetogenic effect of the SNPs rs7903146 and rs12255372 in *TCF7L2* is mitigated by lifestyle intervention (9,10). Changes in BMI and fat depots though were not reported in the DPS and the DPP; therefore, we cannot draw conclusions as to how changes in body weight influence the outcome in these studies. However, it may be speculated that smaller reductions in BMI and body fat due to the risk allele may not necessarily influence type 2 diabetes incidence, at least within the 3- to 4-year observation period.

We currently have no explanation for the conflicting findings with regard to the phenotype of *TCF7L2* SNP carriers in cross-sectional settings (9,10,12) versus our longitudinal setting. In the present study, the intervention was applied to all individuals so that each individual served as his/her own historic control subject. This approach may explain the different findings of studies that are fully randomized.

The effects of *TCF7L2* on body fat found in this study need replication in other larger cohorts and longer-term lifestyle intervention studies to verify their clinical relevance. These studies should include a control group without weight loss and subjects not at high risk for diabetes. In addition, studies at the molecular level should also be undertaken to identify the possible mechanisms of how *TCF7L2* influences body fat change.

In conclusion, we show that diabetes-associated variation in *TCF7L2* influences changes in BMI and body fat and thus predicts the success of lifestyle intervention in terms of weight loss. Therefore, *TCF7L2* represents a gene that influences individual susceptibility toward environmental factors. The mechanisms of how the variants interact with environmental factors to influence BMI are not understood and need further investigation.

ACKNOWLEDGMENTS

This study was supported by a grant from the German Research Foundation (FR1561/5-1).

No potential conflicts of interest relevant to this article were reported.

We thank all study participants for their cooperation. We gratefully acknowledge the excellent technical assis-

tance of Anna Bury, Alke Guirguis, Melanie Weisser, and Roman Werner.

REFERENCES

1. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 2006;38:320–323
2. Saxena R, Gianniny L, Burtt NP, Lyssenko V, Giuducci C, Sjogren M, Florez JC, Almgren P, Isomaa B, Orho-Melander M, Lindblad U, Daly MJ, Tuomi T, Hirschhorn JN, Ardlie KG, Groop LC, Altshuler D. Common single nucleotide polymorphisms in TCF7L2 are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals. Diabetes 2006;55:2890–2895
3. Schafer SA, Tschritter O, Machicao F, Thamer C, Stefan N, Gallwitz B, Holst JJ, Dekker JM, t'Hart LM, Nijpels G, van Haeften TW, Haring HU, Fritsche A. Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms. Diabetologia 2007;50:2443–2450
4. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, Sjogren M, Ling C, Eriksson KF, Lethagen AL, Mancarella R, Berglund G, Tuomi T, Nilsson P, Del Prato S, Groop L. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. J Clin Invest 2007;117:2155–2163
5. Reinehr T, Friedel S, Mueller TD, Toschke AM, Hebebrand J, HinneyA. Evidence for an influence of TCF7L2 polymorphism rs7903146 on insulin resistance and sensitivity indices in overweight children and adolescents during a lifestyle intervention. Int J Obes (Lond) 2008;32:1521–1524
6. Liu PH, Chang YC, Jiang YD, Chen WJ, Chang TJ, Kuo SS, Lee KC, Hsiao PC, Chiu KC, Chuang LM. Genetic variants of TCF7L2 are associated with insulin resistance and related metabolic phenotypes in Taiwanese adolescents and Caucasian young adults. J Clin Endocrinol Metab 2009;94:3575–3582
7. Marzi C, Huth C, Kolz M, Grallert H, Meisinger C, Wichmann HE, Rathmann W, Herder C, Illig T. Variants of the transcription factor 7-like 2 gene (TCF7L2) are strongly associated with type 2 diabetes but not with the metabolic syndrome in the MONICA/KORA surveys. Horm Metab Res 2007;39:46–52
8. Musso G, Gambino R, Pacini G, Pagano G, Durazzo M, Cassader M. Transcription factor 7-like 2 polymorphism modulates glucose and lipid homeostasis, adipokine profile, and hepatocyte apoptosis in NASH. Hepatology 2009;49:426–435
9. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 2006;355:241–250
10. Wang J, Kuusisto J, Vanttinen M, Kuulasmaa T, Lindstrom J, Tuomilehto J, Uusitupa M, Laakso M. Variants of transcription factor 7-like 2 (TCF7L2) gene predict conversion to type 2 diabetes in the Finnish Diabetes Prevention Study and are associated with impaired glucose regulation and impaired insulin secretion. Diabetologia 2007;50:1192–1200
11. Cauchi S, Choquet H, Gutierrez-Aguilar R, Capel F, Grau K, Proenca C, Dina C, Duval A, Balkau B, Marre M, Potoczna N, Langin D, Horber F, Sorensen TI, Charpentier G, Meyre D, Froguel P. Effects of TCF7L2 polymorphisms on obesity in European populations. Obesity (Silver Spring) 2008;16:476–482
12. Helgason A, Palsson S, Thorleifsson G, Grant SF, Emilsson V, Gunnarsdottir S, Adeyemo A, Chen Y, Chen G, Reynisdottir I, Benediktsson R, Hinney A, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Schafer H, Faruque M, Doumatey A, Zhou J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Sigurdsson G, Hebebrand J, Pedersen O, Thorsteinsdottir U, Gulcher JR, Kong A, Rotimi C, Stefansson K. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. Nat Genet 2007;39:218–225
13. Cauchi S, Meyre D, Dina C, Choquet H, Samson C, Gallina S, Balkau B, Charpentier G, Pattou F, Stetsyuk V, Scharfmann R, Staels B, Fruhbeck G, Froguel P. Transcription factor TCF7L2 genetic study in the French population: expression in human beta-cells and adipose tissue and strong association with type 2 diabetes. Diabetes 2006;55:2903–2908
14. Kovacs P, Berndt J, Ruschke K, Kloting N, Schon MR, Korner A, Stumvoll M, Bluher M. TCF7L2 gene expression in human visceral and subcutaneous adipose tissue is differentially regulated but not associated with type 2 diabetes mellitus. Metabolism 2008;57:1227–1231
15. Cawthorn WP, Heyd F, Hegyi K, Sethi JK. Tumour necrosis factor-alpha inhibits adipogenesis via a beta-catenin/TCF4(TCF7L2)-dependent pathway. Cell Death Differ 2007;14:1361–1373
16. Ross SE, Hemati N, Longo KA, Bennett CN, Lucas PC, Erickson RL, MacDougald OA. Inhibition of adipogenesis by Wnt signaling. Science 2000;289:950–953
17. Ross SE, Erickson RL, Gerin I, DeRose PM, Bajnok L, Longo KA, Misek DE, Kuick R, Hanash SM, Atkins KB, Andresen SM, Nebb HI, Madsen L, Kristiansen K, MacDougald OA. Microarray analyses during adipogenesis: understanding the effects of Wnt signaling on adipogenesis and the roles of liver X receptor alpha in adipocyte metabolism. Mol.Cell Biol 2002;22:5989–5999
18. Mani A, Radhakrishnan J, Wang H, Mani A, Mani MA, Nelson-Williams C, Carew KS, Mane S, Najmabadi H, Wu D, Lifton RP. LRP6 mutation in a family with early coronary disease and metabolic risk factors. Science 2007;315:1278–1282
19. Haupt A, Thamer C, Machann J, Kirchhoff K, Stefan N, Tschritter O, Machicao F, Schick F, Haring HU, Fritsche A. Impact of variation in the FTO gene on whole body fat distribution, ectopic fat, and weight loss. Obesity (Silver Spring) 2008;16:1969–1972
20. Schafer S, Kantartzis K, Machann J, Venter C, Niess A, Schick F, Machicao F, Haring HU, Fritsche A, Stefan N. Lifestyle intervention in individuals with normal versus impaired glucose tolerance. Eur J Clin Invest 2007;37:535–543
21. Machann J, Thamer C, Schnoedt B, Haap M, Haring HU, Claussen CD, Stumvoll M, Fritsche A, Schick F. Standardized assessment of whole body adipose tissue topography by MRI. J Magn Reson Imaging 2005;21:455–462
22. Zhang C, Qi L, Hunter DJ, Meigs JB, Manson JE, van Dam RM, Hu FB. Variant of transcription factor 7-like 2 (TCF7L2) gene and the risk of type 2 diabetes in large cohorts of U.S. women and men. Diabetes 2006;55:2645–2648