Brief Genetics Report

Polymorphism in the Transcription Factor 7-Like 2 (*TCF7L2*) Gene Is Associated With Reduced Insulin Secretion in Nondiabetic Women

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Recently, the transcription factor 7-like 2 (*TCF7L2*) gene on chromosome 10q25.2 has been linked with type 2 diabetes among Caucasians, with disease associations noted for single nucleotide polymorphisms (SNPs) rs12255372 and rs7903146. To investigate mechanisms by which *TCF7L2* could contribute to type 2 diabetes, we examined the effects of these SNPs on clinical and metabolic traits affecting glucose homeostasis in 256 nondiabetic female subjects (138 European Americans and 118 African Americans) aged 7–57 years. Outcomes included BMI, percent body fat, insulin sensitivity (S_i), acute insulin response to glucose (AIR_g), and the disposition index (DI). Homozygosity for the minor allele (TT) of SNP rs12255372 occurred in 9% of individuals and was associated with a 31% reduction in DI values in a recessive model. The at-risk allele TT was also associated with lower AIR_g adjusted for S_i in both ethnic groups, whereas rs12255372 genotype was not associated with measures of adiposity or with S_i. The T allele of rs12255372 was also associated with increased prevalence of impaired fasting glucose. Genotypes at rs7903146 were not associated with any metabolic trait. Lower S_i and higher AIR_g observed in the African-American compared with the European-American subgroup could not be explained by the *TCF7L2* genotype. Our data suggest that the *TCF7L2* gene is an important factor regulating insulin secretion, which could explain its association with type 2 diabetes. *Diabetes* 55:3630–3634, 2006

Type 2 diabetes is a heterogeneous disorder characterized by insulin resistance combined with defects in insulin secretion (1). Genetic factors are suspected to affect both insulin secretion and insulin resistance but the causative genes remain elusive (2,3). Genome-wide linkage scans have localized regions on several chromosomes harboring type 2 diabetes susceptibility genes (4); however, with few exceptions, most identified genes confer small to moderate risk or have yielded inconsistent results in replication efforts (5,6). Intronic variation in the transcription factor 7-like 2 (*TCF7L2*) gene located on chromosome 10q has recently been associated with a twofold increase in risk for type 2 diabetes in an Icelandic population. This finding has been replicated in Danish and U.S. Caucasian cohorts (7). Allele T of single nucleotide polymorphisms (SNPs) rs12255372 and rs7903146 in the *TCF7L2* gene were strongly correlated with the original microsatelite marker linked to type 2 diabetes risk, and variation within this gene accounted for 21% of type 2 diabetes risk (7). The mechanism of action of the *TCF7L2* gene with respect to the pathogenesis of type 2 diabetes is not known.

If variants in the *TCF7L2* gene influence susceptibility to type 2 diabetes, they may be associated with insulin resistance and/or impaired insulin secretion. Abnormalities in insulin action and secretion precede the development of overt type 2 diabetes and represent quantitative traits that can help identify the mechanism conferring increased risk for the disease (8). The disposition index (DI), a parameter derived from the frequently sampled intravenous glucose tolerance test (fsIVGTT), assesses the adequacy of the insulin secretory response in light of the prevailing degree of insulin sensitivity or resistance. Relatively low and/or falling DI values identify individuals with increased risk of type 2 diabetes (9).

The aim of the current study was to investigate whether variation in the *TCF7L2* gene was associated with insulin resistance, impaired insulin secretion, or low DI values. To this end, we genotyped SNPs rs12255372 and rs7903146 of the *TCF7L2* gene in a biethnic group of nondiabetic female subjects who underwent a fsIVGTT.

RESEARCH DESIGN AND METHODS

Subjects included 256 nondiabetic female subjects, both European Americans and African Americans, recruited through local advertisement and word-of-mouth from the Birmingham, Alabama, metropolitan area. Responding volunteers meeting inclusion criteria were sequentially enrolled and studied. Inclusion criteria assured they were healthy, were not on medications known to affect metabolism, and had fasting glucose <126 mg/dl. Subjects with fasting blood glucose >100 mg/dl were considered as having impaired fasting glucose (IFG) (10). Ethnicity was self-defined. Subjects provided written informed consent, and the study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham.

fsIVGTT. Subjects were admitted to the general clinical research center, and, the following morning, a fsIVGTT was performed as described by Bergman

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AIR_g, acute insulin response to glucose; DI, disposition index; fsIVGTT, frequently sampled intravenous glucose tolerance test; IFG, impaired fasting glucose; SNP, single nucleotide polymorphism.

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TABLE 1
Clinical characteristics by ethnicity

Clinical characteristics	European Americans	African Americans
n	138	118
Age (years)	34 ± 13	31 ± 12*
IFG [*n* (%)]	13 (9.4)	11 (9.3)
BMI (kg/m^2)	26.8 ± 4.4	27.4 ± 4.0
Percent fat mass	39.2 ± 7.3	37.2 ± 7.7*
Fasting glucose (mg/dl)	90.8 ± 7.3	88.6 ± 6.9*
Fasting insulin (μU/ml)	10.5 ± 1.4	11.7 ± 1.4*
$S_i \times 10^{-4}$ (min · μU^{-1} · ml^{-1})	3.71 (3.36–4.12)	2.38 (2.16–2.67)*
AIR_g (μU/ml per 10 min)	415 (372–466)	925 (828–1,035)*
DI ($S_i \times AIR_g$)	1,480 (1,324–1,683)	2,121 (1,896–2,378)*

Data are *n* (%), means ± SE, or geometric means (95% CI). *$P < 0.05$ compared with European Americans. *n* (%) refers to the number and percentage of subjects with IFG.

(11). At time 0, glucose (25% dextrose; 11.4 g/m^2) was administered intravenously. An intravenous bolus of 0.02 units insulin/kg was administered 20 min after the glucose dose. Blood samples were collected at the following time points relative to glucose administration at 0 min: 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min. Serum samples were analyzed for glucose and insulin, and values were entered into the Minmod computer program (version 3.0; Richard N. Bergman, Department of Physiology and Biophysics, University of Southern California, Los Angeles, CA). The model analyzes the dynamic relationship between blood glucose and insulin concentrations to derive an insulin sensitivity index (S_i), with decreasing values indicative of greater degrees of insulin resistance. The acute insulin response to glucose (AIR_g) is the integrated incremental area under the curve for insulin during the first 10 min of the test (12). DI is defined as the product of $S_i \times AIR_g$ and reflects whether the insulin secretory response is sufficiently robust to compensate for the prevailing degree of insulin resistance.

Body composition. Total body-fat mass and soft lean-tissue mass were assessed by whole-body dual-energy X-ray absorptiometry using a General Electric Lunar Prodigy densitometer (General Electric Lunar, Madison, WI).

Assays. Glucose was measured using an Ektachem DT II System (Johnson and Johnson Clinical Diagnostics, Rochester, NY). Plasma insulin levels were measured by radioimmunoassay using standard commercial kits (Linco Research, St. Charles, MO).

Genotyping. Genotyping for SNPs rs12255372 and rs7903146 utilized the real-time allele discrimination method using TaqMan Allelic Discrimination Assays (Applied Biosystems, Foster City, CA). The TaqMan genotyping reaction was run on an 7900HT Fast Real-Time PCR (Applied Biosystems) and MX3000 (Stratagene, Cedar Creek, TX). Results were confirmed by pyrosequencing (13).

Statistical analyses. Descriptive data are presented as means ± SD. Because of skewed distributions, fasting insulin, S_i, AIR_g, and DI were logarithmically transformed, and geometric means and 95% CIs are presented for these variables. Hardy-Weinberg equilibrium, estimated haplotype frequencies, and r^2 linkage disequilibrium coefficients were assessed by methods implemented in Arlequin program 3.01 (Schneider S, Roessli D, Excoffier L, University of Geneva, Switzerland). Allele and haplotype frequency comparisons among groups were performed by the χ^2 test. ANCOVA and ordinary least-squares regression were used for S_i, AIR_g, and DI as dependent variables and age, BMI, percent fat mass, and ethnicity as independent covariates. Associations were tested under additive, dominant, and recessive genetic models. In the recessive model, homozygosity for the major allele and the heterozygous state were coded as 0 and homozygosity for the T allele as 1. For the dominant model, homozygosity for the major allele was coded as 0, and the heterozygous state and homozygosity for the minor allele were coded as 1. In the additive model, homozygosity for major allele was coded as 0; heterozygosity was coded as 1 and homozygosity for the minor allele as 2. The statistical analysis was performed using SAS 8.2 (SAS Institute, Cary, NC). A *P* value <0.05 was considered statistically significant.

RESULTS

The study group included 256 unrelated nondiabetic female subjects (138 European Americans and 118 African Americans) aged 7–57 years. Table 1 summarizes clinical characteristics by ethnicity. Compared with European Americans, African Americans were younger, had a lower percentage fat mass, and lower fasting glucose but higher fasting insulin ($P < 0.05$). African Americans also had lower S_i, higher AIR_g, and higher DI compared with European Americans, as previously reported (14). In univariate analysis, S_i was inversely correlated with BMI ($r = -0.44$, $P < 0.01$) and percentage fat mass ($r = -0.26$, $P < 0.01$) but was not related to age. Insulin secretion, measured as AIR_g, was not related to measures of adiposity but was inversely related to age ($r = -0.21$, $P < 0.01$) and S_i ($r = -0.38$, $P < 0.01$).

Table 2 shows the genotype frequencies for SNPs rs12255372 and rs7903146. No significant deviation from Hardy-Weinberg equilibrium was observed in either the European-American or African-American populations for either SNP ($P = 0.66$ for rs12255372 and $P = 0.88$ for rs7903146). The minor allele (T) frequency was 0.12 for SNP rs12255372 and 0.14 for SNP rs7903146; there were no significant differences in allele or genotype frequencies between European Americans and African Americans. Genotype frequencies were similar to those reported in Icelandic, Danish, and U.S. populations (7). However, a difference between the European-American and African-American populations was found when we tested for association between alleles for the two SNPs. While a strong correlation was observed ($r^2 = 0.77$) in the European-American population, a very low correlation was found in the African-American population ($r^2 = 0.008$). These correlation coefficients are very similar to the coefficients observed by the International Haplotype Map study in the Utah residents with ancestry from Northern and Western Europe (CEU) and in the Yoruban (Ibadan, Nigeria) population in Africa (www.hapmap.org), which is consistent with the European and African genetic inheritance of our populations.

Associations between metabolic traits and the two SNPs in the *TCF7L2* gene were then examined. As shown in Table 3, subgroups based on genotype for SNP rs12255372 did not display significant differences in BMI, percent fat mass, fasting plasma glucose, fasting plasma insulin, or S_i

TABLE 2
Genotype frequencies of SNPs rs12255372 and rs7903146 in European Americans and African Americans

Genotype	European Americans	African Americans	*P* value
n	138	118	
rs12255372			
G/G	68 (0.49)	60 (0.50)	0.96
G/T	57 (0.41)	47 (0.39)	
T/T	13 (0.09)	11 (0.09)	
Allele frequency			
G	193 (0.70)	167 (0.71)	
T	83 (0.30)	69 (0.29)	
rs7903146			
C/C	63 (0.45)	54 (0.45)	0.82
C/T	59 (0.42)	53 (0.44)	
T/T	16 (0.11)	11 (0.09)	
Allele frequency			
C	185 (0.67)	161 (0.68)	
T	91 (0.33)	75 (0.32)	

Data are *n* (frequency). *P* value refers to genotype distribution between groups.

TABLE 3
Clinical characteristics by ethnicity and SNP rs12255372 genotype

Clinical characteristics	European Americans			African Americans		
	GG	GT	TT	GG	GT	TT
n	68	57	13	60	47	11
Age (years)	33 ± 12	36 ± 13	36 ± 13	28 ± 12	34 ± 12*	33 ± 10*
IFG [*n* (%)]	4 (5)	8 (14)	1 (7)	3 (5)	7 (14)	1 (9)
BMI (kg/m^2)	26.6 ± 3.8	26.5 ± 4.2	28.6 ± 7.4	27.1 ± 4.3	27.9 ± 3.8	27.6 ± 3.5
Percent fat mass	39.6 ± 7.2	38.3 ± 7.5	40.7 ± 7.4	36.4 ± 7.7	38.5 ± 8.0	35.9 ± 5.6
Fasting glucose (mg/dl)	90.4 ± 7.3	91.0 ± 7.0	91.3 ± 8.8	88.7 ± 6.2	88.5 ± 8.1	88.7 ± 6.0
Fasting insulin (μU/ml)	10.4 ± 1.3	10.6 ± 1.5	10.5 ± 1.5	11.5 ± 1.4	11.8 ± 1.5	12.1 ± 1.5
$S_i \times 10^{-4}$ (min · μU^{-1} · ml^{-1})	3.52 (3.09–4.08)	4.05 (3.43–4.80)	3.17 (2.19–4.47)	2.59 (2.22–3.01)	2.25 (1.91–2.68)	2.00 (1.34–2.86)
AIR_g (μU · ml^{-1} · min^{-1})	428 (364–505)	428 (358–513)	317 (223–451)	943 (801–1,126)	915 (775–1,090)	828 (595–1,153)
DI ($S_i \times AIR_g$)	1,465 (1,239–1,763)	1,652 (1,384–2,008)	962 (714–1,315)*	2,344 (1,983–2,798)	1,978 (1,695–2,338)	1,587 (1,074–2,356)*

Data are *n* (%), means ± SE, or geometric means (95% CI). *$P < 0.05$ for the comparison with major allele. *n* (%) refers to the number and percentage of subjects with IFG.

in either European Americans or African Americans. Unadjusted AIR_g values tended to be lower in European Americans and African Americans homozygous for TT. These differences achieved statistical significance after adjusting for S_i, ethnicity, and age in the pooled population ($R^2 = 0.50$, $P < 0.01$). Data were best fitted by a recessive genetic model. Homozygosity for the SNP rs12255372 T allele had lower adjusted AIR_g (mean 474 [95% CI 383–527]) compared with normal variant and heterozygous (637 [595–683], $P < 0.01$). In this model, SNP rs12255372 explained 2.1% of AIR_g variability. An effect of genotype was also observed for DI; homozygosity for the SNP rs12255372 minor T allele in the pooled study population was associated with markedly lower DI values when compared with either the normal variant or heterozygous subgroups (Table 3). The effect of SNP rs12255372 genotype on DI remained statistically significant after adjusting for the effects of ethnicity and age in a recessive model (1,269 [998–1,615] vs. 1,864 [1,724–2,015], TT vs. GG/GT, respectively, $P < 0.01$).

In stratified analysis by race, homozygosity for the T allele was similarly associated with significantly lower DI in both European Americans (969 [95% CI 676–1,389]) and African Americans (1,591 [1,116–2,197]) compared with the mean values in the normal variant and heterozygous group (1,573 [1,399–1,768] for European Americans vs. 2,228 [2,201–2,497] for African Americans, $P < 0.05$ for both comparisons). Among European Americans, these differences were still significant after adjusting for the effect of age (mean DI for minor allele 992 [95% CI 698–1,310] vs. 1,569 [1,400–1,759] for normal variant and heterozygous, $P < 0.05$). However, among African Americans, the association with low DI values lost statistical significance after adjusting for age (Fig. 1).

Examination of Tables 1 and 3 reveals that 13 European Americans and 11 African Americans had IFG. Prevalence

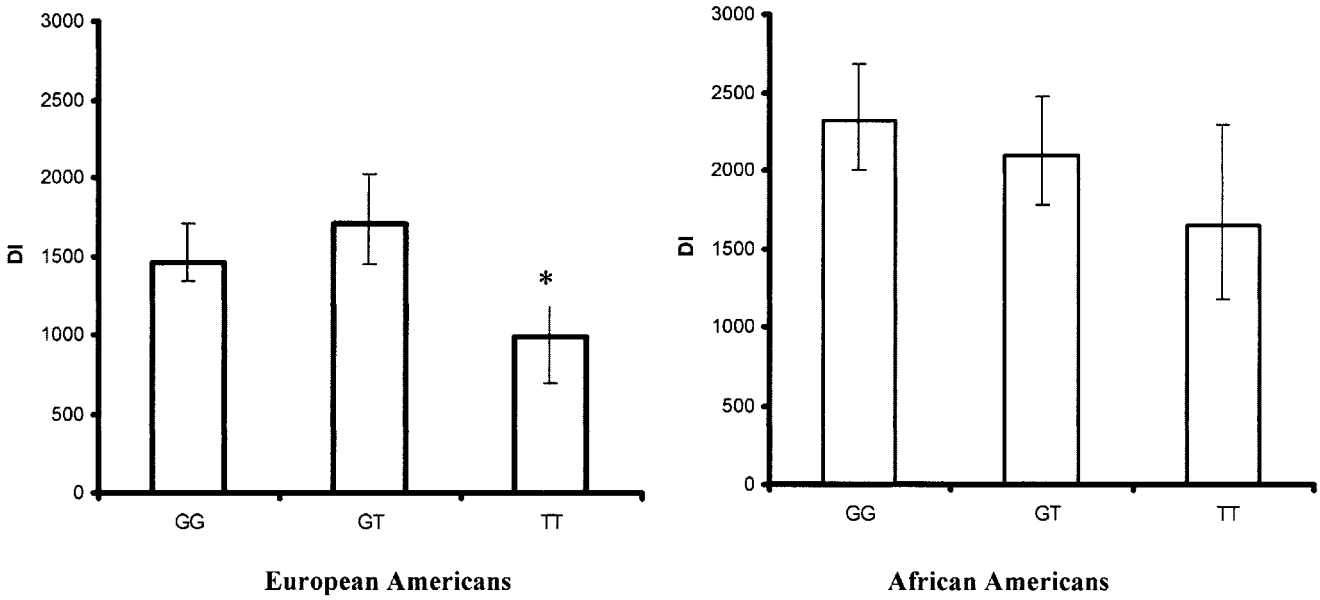

FIG. 1. Effect of SNP rs12255372 genotype on DI, adjusted for age, for European-American ($n = 138$) and African-American ($n = 118$) women. Values represent geometric means, and bars indicate 95% CIs. *$P < 0.05$ compared with GG or GT.

of IFG was disproportionately higher among rs12255372 T allele carriers in both ethnic groups (12% among European Americans and 13% among African Americans) compared with non–T allele carriers (5% for European Americans and African Americans; $\chi^2 = 4.59$, $P < 0.05$).

Subgroups based on SNP rs7903146 genotype (CC, CT, and TT) were not associated with statistically significant differences for any of the metabolic characteristics, including DI (online appendix [available at http://diabetes.diabetesjournals.org]). The lack of influence of the rs7903146 genotype on the various outcomes was similarly apparent after stratified analysis by race.

DISCUSSION

TCF7L2 has recently been implicated as an important type 2 diabetes gene in three populations of European Caucasian ancestry (7). We have investigated whether *TCF7L2* gene variations are associated with various clinical and metabolic traits in nondiabetic female subjects to gain insight into mechanisms underlying the type 2 diabetes risk. In addition, the current studies involved both European-American and African-American sample populations. We demonstrated for the first time that SNP rs12255372 in the *TCF7L2* gene was significantly associated with β-cell function. Specifically, homozygosity for the minor allele (TT) of SNP rs12255372 was associated with significantly lower DI and AIR_g adjusted for S_i. These data indicate that *TCF7L2* influences insulin secretion and may affect susceptibility for type 2 diabetes by modulating the adequacy of insulin secretion to compensate for the prevailing degree of insulin resistance. Furthermore, the data suggest that *TCF7L2* likely represents a type 2 diabetes susceptibility gene in African- and European-derived populations.

Longitudinal studies indicate that both insulin resistance and impaired early-phase insulin secretion precede the development of type 2 diabetes and worsens during progression to overt diabetes (15). In the present study, we did not find any relationship between S_i and SNPs rs12255372 or 7903146, making it unlikely that these variants increased the risk of type 2 diabetes by contributing to insulin resistance. On the other hand, homozygosity for the T allele of rs12255372 was associated with significantly lower insulin secretory capacity in nondiabetic female subjects relative to the degree of insulin resistance. Thus, the *TCF7L2* gene is influencing insulin secretory capacity, and it is this mechanism that may explain its association with type 2 diabetes in European Americans. Recent data from the longitudinal Insulin Resistance Atherosclerosis Study showed that changes in AIR_g were more important in determining glucose tolerance status at follow-up than were changes in S_i (16). Furthermore, evidence indicates that β-cell function may be more highly determined by heritable factors compared with other known pathogenic traits involved in type 2 diabetes (17). Based on our data, we posit that *TCF7L2* is an important gene that contributes to heritability of insulin secretion and type 2 diabetes risk. This formulation is also consistent with our observation that homo- and heterozygous carriers of the rs12255372 T allele display a significantly increased prevalence of IFG. However, it is not clear why heterozygotes are more likely to have IFG since only homozygosity for the T allele was associated with impaired insulin secretion. We are also unsure concerning the mechanisms by which the *TCF7L2* gene can affect insulin secretion, although this transcription factor may potentially affect pathways involved in the regulation of β-cell function, including incretin synthesis and secretion (18).

In the recent report by Grant et al. (7), both rs12255372 and rs7903146 in the*TCF7L2* gene were associated with type 2 diabetes in European-derived Caucasian populations. However, we observed that only rs12255372 was associated with measures of reduced insulin secretion, while SNP rs7903146 genotypes were not associated with any of the metabolic phenotypes, including DI or AIR_g. It may be relevant that, in Caucasians, Grant et al. (7) observed that rs7903146 was less well correlated than rs12255372 with the microsatellite DG10S478, which first drew their attention to this chromosomal region in the context of a whole-genome scan. Also, it is important to consider that Grant et al. (7) assessed type 2 diabetes as the phenotype, not metabolic traits. The number of subjects in the current study may not have provided sufficient power to demonstrate a significant association between SNP rs7903146 with S_i, DI, or AIR_g adjusted for S_i. It is also important to consider the low degree of linkage disequilibrium between the two SNPs in African Americans and Yorubans. Since only rs12255372 was associated with impaired insulin secretion, it is predictable that only rs12255372, and not rs7903146, would be associated with type 2 diabetes in African-derived populations.

In conclusion, the present study suggests that the *TCF7L2* gene participates in the regulation of insulin secretion, and this can explain its role as an important type 2 diabetes susceptibility gene. Further biological and/or functional evidence is needed to clarify the mechanistic role of this transcription factor in the pathophysiology of impaired insulin secretion and type 2 diabetes.

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REFERENCES

1. Chiasson JL, Rabasa-Lhoret R: Prevention of type 2 diabetes: insulin resistance and β-cell function. *Diabetes* 53 (Suppl. 3):S34–S38, 2004
2. DeFronzo RA: Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes gene. *Diabetes Rev* 5:177–269, 1997
3. Stern MP: Strategies and prospects for finding insulin resistance genes. *J Clin Invest* 106:323–327, 2000
4. Stern MP: The search for type 2 diabetes susceptibility genes using whole-genome scans: an epidemiologist's perspective. *Diabetes Metab Res Rev* 18:106–113, 2002
5. Hansen L, Pedersen O: Genetics of type 2 diabetes mellitus: status and perspectives. *Diabetes Obes Metab* 2:122–135, 2005
6. McCarthy MI: Progress in defining the molecular basis of type 2 diabetes mellitus through susceptibility-gene identification. *Hum Mol Genet* 13: R33–R41, 2004
7. 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* 38:320–323, 2006
8. Ferrannini E, Nannipieri M, Williams K, Gonzales C, Haffner SM, Stern MP: Mode of onset of type 2 diabetes from normal or impaired glucose tolerance. *Diabetes* 53:160–165, 2004

9. Lyssenko V, Almgren P, Anevski D, Perfekt R, Lahti K, Nissen M, Isomaa B, Forsen B, Homstrom N, Saloranta C, Taskinen MR, Groop L, Tuomi T, the Botnia Study Group: Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. *Diabetes* 54:166–174, 2005
10. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
11. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest* 68:1456–1467, 1981
12. Pacini G, Bergman, RN: MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. *Comput Methods Programs Biomed* 23:113–122, 1986
13. Ahmadian A, Ehn M, Hober S: Pyrosequencing: history, biochemistry and future. *Clin Chim Acta* 363:83–94, 2006
14. Gower BA: Syndrome X in children: influence of ethnicity and visceral fat. *Am J Hum Biol* 2:249–257, 1999
15. Haffner SM, Miettinen H, Gaskill SP, Stern MP: Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican Americans. *Diabetes* 44:1386–1391, 1995
16. Festa A, Williams K, D'Agostino R Jr, Wagenknecht LE, Haffner SM: The natural course of β-cell function in nondiabetic and diabetic individuals: the Insulin Resistance Atherosclerosis Study. *Diabetes* 55:1114–1120, 2006
17. Poulsen P, Levin K, Petersen I, Christensen K, Beck-Nielsen H, Vaag A: Heritability of insulin secretion, peripheral and hepatic insulin action, and intracellular glucose partitioning in young and old Danish twins. *Diabetes* 54:275–283, 2005
18. Yi F, Brubaker PL, Jin T: TCF-4 mediates cell type-specific regulation of proglucagon gene expression by beta-catenin and glycogen synthase kinase-3beta. *J Biol Chem* 280:1457–1464, 2005