Transcription Factor 7-Like 2 (*TCF7L2*) Polymorphism and Context-Specific Risk of Type 2 Diabetes in African American and Caucasian Adults

The Atherosclerosis Risk in Communities Study

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OBJECTIVE—Although variants in the transcription factor 7-like 2 (*TCF7L2*) gene are consistently associated with type 2 diabetes, large population-based studies of African Americans are lacking. Moreover, few studies have investigated the effects of *TCF7L2* on type 2 diabetes in the context of metabolic risk factors of type 2 diabetes.

RESEARCH DESIGN AND METHODS—We investigated the association between the *TCF7L2* rs7903146 polymorphism and type 2 diabetes in 2,727 African American and 9,302 Caucasian participants without diabetes who were inducted into the Atherosclerosis Risk in Communities study in 1987–1989 and followed for 9 years.

RESULTS—A total of 485 and 923 cases of type 2 diabetes were identified in African Americans and Caucasians, respectively. Compared with homozygous CC individuals, heterozygous CT and homozygous TT individuals had higher cumulative incidence of type 2 diabetes over 9 years of follow-up: 11.3% (95% CI 10.2–12.4) vs. 21.1% (20.8–21.4) and 27.9% (19.3–36.5) in African Americans, respectively, and 9.7% (8.8–10.6) vs. 11.3% (10.2–12.4) and 13.6% (11.1–16.1), respectively, in Caucasians. Individuals with the risk allele had the highest hazards of diabetes if they were obese and had low HDL cholesterol, followed by individuals with any one and none of the traits.

CONCLUSIONS—Our study provides the first significant evidence of association between the *TCF7L2* rs7903146 polymorphism and type 2 diabetes risk in a large African American population and also demonstrates that the diabetes risk conveyed by the rs7903146 risk allele is substantially increased in the context of some metabolic risk factors for type 2 diabetes. Our study findings need to be replicated in other large, population-based studies. ***Diabetes* 58:285–289, 2009**

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Type 2 diabetes is characterized by insulin resistance and defects in insulin secretion as a result of β-cell dysfunction (1) resulting from the interplay of genetic and environmental factors (2). The transcription factor 7-like 2 (*TCF7L2*) gene, a Wnt signaling-associated transcription factor located on chromosome 10q25, has emerged as a consistently replicated susceptibility gene for type 2 diabetes (3–5). The T-allele at single nucleotide polymorphism (SNP) rs7903146 has been described as either the causal risk variant or the closest correlate to an unidentified functional variant (6), possibly impairing glucagon-like peptide-1–induced insulin secretion (7), but the exact mechanism is still under investigation.

Although the *TCF7L2* effect is consistently observed across ethnically diverse populations (3,4), studies conducted in African Americans have been of small sample size and results have been inconsistent (4–6,8,9). Moreover, *TCF7L2* gene–environment interaction assessment has been limited. Although previous studies have demonstrated effect modification by BMI (8,10), modifications by other metabolic risk factors have been largely unexplored.

In this study, we investigated whether the rs7903146 SNP of the *TCF7L2* gene is associated with type 2 diabetes in a large community-based cohort of African American and Caucasian middle-aged adults participating in the Atherosclerosis Risk in Communities (ARIC) study. A second objective was to evaluate whether the risk of type 2 diabetes was associated with the rs7903146 SNP in the context of metabolic impairments.

RESEARCH DESIGN AND METHODS

Study subjects and phenotype definitions. The ARIC study is an ongoing longitudinal cohort study of cardiovascular and other major diseases among 15,792 men and women aged 45–64 years at baseline (1987–1989) and selected from four U.S. communities: Forsyth County, NC; Jackson, MS; the northwestern suburbs of Minneapolis, MN; and Washington County, MD. By design, African Americans were oversampled at the Forsyth County site and exclusively sampled in Jackson and thus constituted 27% of the baseline cohort. The sampling procedures and methods used in ARIC have been described in detail elsewhere (11).

We excluded ARIC participants who were not African American or Caucasian (n = 48), African Americans from Minnesota and Maryland field centers (n = 55), participants with prevalent diabetes (n = 1,863), participants with missing information on incident diabetes (n = 1,026), and participants with missing genotype data or who did not provide consent for the use of DNA (n = 771). After these exclusions, 12,029 baseline examination participants (2,727 African Americans and 9,302 Caucasians) were available for analysis.

TABLE 1
Selected characteristics of the ARIC study participants at baseline, presented by race and genotype status

	African American				Caucasian			
	CC	CT	TT	*P*	CC	CT	TT	*P*
n	1,381	1,133	213		4,725	3,783	794	
Age (years)	53 ± 5.83	53 ± 5.60	54 ± 5.83	0.12	54 ± 5.66	54 ± 5.69	54 ± 5.75	0.25
Sex (male)	500 (36.21)	447 (39.45)	81 (38.03)	0.25	2,188 (46.31)	1,746 (46.15)	379 (47.73)	0.71
Family diabetes history	318 (23.03)	295 (26.04)	57 (26.76)	0.16	1,006 (21.29)	846 (22.36)	178 (22.42)	0.45
Predicted diabetes risk*	0.23 ± 0.20	0.20 ± 0.19	0.25 ± 0.22	0.01	0.15 ± 0.15	0.16 ± 0.16	0.17 ± 0.15	0.27
Ever smoked	715 (51.77)	610 (53.89)	117 (54.93)	0.47	2,793 (59.14)	2,241 (59.27)	475 (59.82)	0.94
Leisure-time physical activity	2.08 ± 0.58	2.12 ± 0.59	2.05 ± 0.56	0.22	2.48 ± 0.53	2.48 ± 0.53	2.46 ± 0.53	0.62
Obese	522 (37.80)	393 (34.75)	72 (33.80)	0.22	998 (21.12)	724 (19.16)	141 (17.76)	0.02
BMI (kg/m^2)	29.34 ± 6.11	28.86 ± 5.81	28.55 ± 5.28	0.05	26.73 ± 4.58	26.52 ± 4.60	26.54 ± 4.58	0.09
Waist circumference (cm)	97.97 ± 15.09	96.74 ± 14.38	96.25 ± 13.28	0.06	95.37 ± 12.93	94.74 ± 12.66	94.96 ± 12.67	0.08
Hypertension	700 (51.02)	572 (50.66)	103 (48.58)	0.80	1,154 (24.57)	923 (24.51)	174 (22.03)	0.29
SBP (mmHg)	131.07 ± 21.93	132.19 ± 22.43	129.08 ± 22.07	0.42	119.83 ± 16.48	119.97 ± 17.18	121.17 ± 16.69	0.36
DBP (mmHg)	77.43 ± 10.34	77.44 ± 11.33	76.14 ± 11.05	0.53	70.97 ± 9.17	70.91 ± 9.10	71.37 ± 9.30	0.67
IFG	594 (44.30)	461 (42.25)	87 (41.83)	0.55	1,868 (40.20)	1,560 (41.97)	371 (47.63)	<0.01
Glucose (mmol/l)	5.47 ± 0.56	5.46 ± 0.54	5.47 ± 0.57	0.95	5.45 ± 0.49	5.48 ± 0.50	5.52 ± 0.52	<0.01
Insulin (μU/ml)	13.82 ± 10.67	12.79 ± 8.78	12.62 ± 8.68	0.02	10.24 ± 7.60	9.83 ± 7.27	9.88 ± 8.10	0.04
HOMA-IR†	3.45 ± 2.90	3.18 ± 2.37	3.15 ± 2.33	0.03	2.54 ± 2.05	2.45 ± 1.97	2.47 ± 2.18	0.12
Triglycerides (mg/dl)	104.06 ± 62.50	105.63 ± 78.38	104.88 ± 58.04	0.86	130.33 ± 76.91	128.73 ± 76.80	130.75 ± 83.63	0.59
Low HDL	400 (29.59)	321 (28.92)	59 (28.37)	0.90	1,799 (38.13)	1,436 (38)	306 (38.59)	0.95
HDL (mg/dl)	56.51 ± 17.77	56.45 ± 17.96	55.48 ± 17.23	0.74	51.41 ± 16.78	51.75 ± 16.95	51.10 ± 16.50	0.49
LDL (mg/dl)	136.84 ± 42.65	135.78 ± 41.54	136.33 ± 47.07	0.83	137.60 ± 37.46	136.7 ± 37.54	137.49 ± 37.70	0.54
One metabolic risk factor‡	526 (38.56)	436 (39.03)	83 (39.71)	0.93	1,719 (36.43)	1,300 (34.42)	295 (37.20)	0.10
Two metabolic risk factors‡	198 (14.52)	139 (12.44)	24 (11.48)	0.24	539 (11.42)	430 (11.38)	76 (9.58)	0.30

Data are means ± SE or *n* (%) unless otherwise indicated. *Probability of developing diabetes over the 9-year follow-up period was predicted by a model including age at baseline, race, parental history of diabetes, fasting glucose, systolic blood pressure, waist circumference, height, HDL cholesterol, and triglycerides (ref. 22). †Calculated as fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (ref. 21). ‡Metabolic risk factors refer to obesity or low HDL cholesterol. DBP, diastolic blood pressure; IFG, impaired fasting glucose; SBP, systolic blood pressure.

The institutional review boards at all participating institutions approved the procedures, and all participants included in the analysis gave informed consent.

Individuals were classified as diabetic if any of the following conditions were met: fasting serum glucose levels ≥7.0 mmol/l (126 mg/dl), nonfasting glucose levels ≥11.1 mmol/l (200 mg/dl), current use of hypoglycemic medications (e.g., insulin or sulfonlyureas), or a self-reported physician diagnosis of diabetes (12). Individuals without diabetes at baseline who subsequently met any of these criteria at visit two, three, or four were considered to have incident type 2 diabetes.

A positive family history of diabetes was defined by participant report of diabetes in either biological parent. Self-reported cigarette smoking was defined as ever smoking versus never smoking, and the information was obtained by a personal interview. BMI was calculated as kilograms divided by the square of height in meters. Individuals with a BMI ≥30 kg/m^2 were classified as obese (13). Elevated waist circumference was defined as waist circumference ≥102 cm in men or ≥88 cm in women (14). Blood pressure at baseline was measured three times using a random zero sphygmomanometer, and the average of the last two measurements was used for this analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or antihypertension medication use (15). Plasma total cholesterol levels, HDL cholesterol, and triglyceride levels were measured by enzymatic methods, and LDL cholesterol was calculated (16). Low HDL was defined as <40 mg/dl in men and <50 mg/dl in women. High LDL was defined as >160 mg/dl, and high triglyceride levels were defined as >200 mg/dl (17). Insulin was measured by radioimmunoassay (^{125}Insulin Kit; Cambridge Medical Diagnostics, Billerica, MA). Physical activity was quantified using a slightly modified version of the Baecke physical activity questionnaire (18) that classified work, sport, and leisure activities into categories ranging from one (low) to five (high). Impaired fasting glucose was defined by a fasting glucose level between 100 and 125 mg/dl (19). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting serum insulin (μU/ml) × fasting glucose (mmol/l)/22.5 (20). Predicted diabetes risk was defined as the probability of developing diabetes over the 9-year follow-up period, which is predicted by a model that includes age at baseline, race, parental history of diabetes, fasting glucose, systolic blood pressure, waist circumference, height, HDL cholesterol, and triglycerides (21).

SNP genotyping. The *TCF7L2* rs7903146 SNP was genotyped by the ARIC central laboratory using Taqman assays (Applied Biosystems, Foster City, CA). Laboratory-designed probes were obtained from Applied Bioystems and primers from Integrated DNA Technologies (Coralville, IA). All PCR reactions took place in optical 384-well reaction plates (Applied Biosystems). Five percent of samples were regenotyped for quality control, and 726 ARIC participants were genotyped in duplicate. The percent agreement was 98%, and the simple κ coefficient was 0.97, indicating a good genotyping quality.

Statistical analysis. All analyses were stratified by race to crudely account for population stratification. To assess whether genotype distribution within each race departed from Hardy-Weinberg equilibrium, a χ^2 goodness-of-fit test was used. We estimated the predicted cumulative incidence/risk of type 2 diabetes over a 9-year follow-up using the Kaplan-Meier approach. We also calculated the risk difference of type 2 diabetes by subtracting the risk among the reference group (i.e., CC carriers) from the risk among the index group (i.e., homozygous TT carriers). We used Cox proportional hazards modeling to estimate the hazard ratios (HRs) and 95% CIs of incident diabetes. The hazard function was formulated on the age scale, and date of diabetes onset was interpolated using blood glucose levels at the visits at each end of the triennial intervals (22). Covariates—including ever smoking, BMI, obesity, hypertension, HDL and LDL cholesterol, and work, sport, and leisure-time physical activity level—were assessed as potential confounders and dismissed from all further analyses. We compared heterozygous CT-genotype and homozygous TT-genotype individuals with CC-genotype individuals, using the rs7903146 CC-genotype as the referent group and the T-allele as the risk variant.

TABLE 2
Genotypic frequency of *TCF7L2* rs7903146 presented by race and incident type 2 diabetes status, cumulative incidence of type 2 diabetes by race and genotype over 9 years of follow-up, and estimated HRs of rs7903146 on type 2 diabetes by race: the ARIC study*

	African American				Caucasian			
Genotype	Controls/cases	Cumulative incidence (%) (95% CI)	HR (95% CI)†	*P*‡	Controls/cases	Cumulative incidence (%) (95% CI)	HR (95% CI)†	*P*‡
n	2,242/485	20.6 (18.7–22.5)			8379/923	10.7 (10.0–11.4)		
CC	1,156 (52)/225 (46)	11.3 (10.2–12.4)	1.00		4,295 (51)/430 (47)	9.7 (8.8–10.6)	1.00	
CT	921 (41)/212 (44)	21.1 (20.8–21.4)	1.17 (1.02–1.34)	0.03	3,391 (40)/392 (42)	11.3 (10.2–12.4)	1.18 (1.07–1.30)	<0.01
TT	165 (7)/48 (10)	27.9 (19.3–36.5)	1.36 (1.03–1.79)		693 (8)/101(11)	13.6 (11.1–16.1)	1.38 (1.14–1.68)	
T-allele (%)	28/32				29/32			

*The Genotypic distributions were in agreement with Hardy-Weinberg equilibrium in African Americans and Caucasians. †Adjusted for age at baseline, study center, and sex. ‡*P* value for HR from additive models.

Variables taking on the values zero for genotype CC, one for genotype CT, and two for genotype TT were used to test for additive genetic effects.

The assessment of departure from additivity in gene-environment interaction analyses has been argued to be more indicative of the underlying biologically causal mechanisms than the assessment of multiplicative interaction (23). Among the three measures of additivity (the interaction contrast ratio [ICR], proportion of disease attributable to interaction, and synergy index), ICR performs best when using a proportional hazards model (24).

Variables were considered as potential effect-measure modifiers if either of the following criteria were met: departures from additivity of effect as assessed by the ICR (23) or an indication of context-specific effects in the previous *TCF7L2* literature. ICRs were quantified as follows: ICR = HR_AB − HR_A − HR_B + 1, where HR_AB represents the joint effect of metabolic exposure and the SNP and HR_A and HR_B represent the main effects of metabolic exposure and the SNP, respectively (23). Thus, ICR refers to the increased risk due to additive interaction between metabolic risk factors and the T-(risk) allele adjusted for age, sex, and study center. Assuming an additive mode of inheritance, the ICR comparing TT with CT is equal to the ICR comparing CT with CC where the metabolic exposure of interest is constant; thus, only one ICR was reported. Departures from zero suggest that the exposure of interest and the SNP interact to cause type 2 diabetes. The HR and the variance-covariance matrix were used to calculate ICR values and their 95% CIs (24). As our interaction analyses indicated obesity and low HDL as possible effect modifiers, we further divided the ARIC population into three mutually exclusive subgroups according to the presence of none, one (obesity only or low HDL only), or both of these two metabolic risk factors.

RESULTS

Selected baseline characteristics of the ARIC study participants without diabetes are presented by race and genotype status in Table 1. A total of 485 (17.8%) and 923 (9.9%) incident type 2 diabetes cases were identified among African American and Caucasian ARIC participants, respectively (Table 2). The rs7903146 T-allele was observed with similar frequency in African American and Caucasian individuals but was more common among incident type 2 diabetes cases than noncases in both races (Table 2). The risk of type 2 diabetes was highest among TT individuals, followed by CT individuals, and lowest among CC individuals in both races (Table 2). As previously documented, the risk of type 2 diabetes was higher in African Americans than in Caucasians with the same genotype.

We identified obesity and low HDL as important effect-measure modifiers, although 95% CIs of some individual ICRs were wide (Table 3; online appendix Table 1, available at http://dx.doi.org/10.2337/db08-0569). Individuals with one or two T-alleles had the highest HRs of developing type 2 diabetes if they were obese and had low HDL, followed by individuals with any one of these two risk factors and lowest among those with none of the traits (Table 4). Homozygous individuals (TT) with two metabolic risk factors had the highest HR of type 2 diabetes (6.04 [95% CI 3.70–9.87] in African Americans and 9.35 [6.72–13.00] in Caucasians) compared with CC individuals with none of these two. A similar trend was observed for risk differences and risks of type 2 diabetes (online

TABLE 3
Association of *TCF7L2* rs7903146 with type 2 diabetes modified by obesity and low HDL cholesterol over 9 years of follow-up in ARIC*

	HR (95% CI) †				
Characteristics	CC genotype	CT genotype	TT genotype	ICR (95% CI)	*P*‡
African-American					
Obesity					
No	1	1.32 (1.08–1.61)	1.74 (1.16–2.61)	−0.05 (−0.66 to 0.57)	0.88
Yes	2.91 (2.25–3.76)	3.18 (2.49–4.07)	3.48 (2.44–4.95)		
Low HDL					
No	1	1.05 (0.87–1.26)	1.10 (0.77–1.58)	0.57 (0.18–0.96)	0.004
Yes	1.45 (1.12–1.88)	2.07 (1.66–2.58)	2.96 (2.08–4.20)		
Caucasian					
Obesity					
No	1	1.21 (1.06–1.37)	1.45 (1.12–1.88)	0.69 (0.10–1.27)	0.02
Yes	3.55 (2.96–4.25)	4.44 (3.76–5.25)	5.56 (4.30–7.19)		
Low HDL					
No	1	1.20 (1.03–1.40)	1.44 (1.06–1.96)	0.27 (−0.11 to 0.66)	0.16
Yes	2.67 (2.21–3.21)	3.14 (2.64–3.74)	3.69 (2.91–4.69)		

*All subgroups had sample sizes of ≥59 and ≥141 in African Americans and Caucasians, respectively. †Adjusted for age at baseline, study center, and sex. ‡*P* value for ICR.

TABLE 4
Association of *TCF7L2* rs7903146 with type 2 diabetes* modified by the number of metabolic risk factors (obesity and low HDL cholesterol) in ARIC

No. of abnormal metabolic traits†	African American			Caucasian		
	CC genotype	CT genotype	TT genotype	CC genotype	CT genotype	TT genotype
None	1	1.14 (0.88–1.48)	1.30 (0.77–2.20)	1	1.19 (0.98–1.44)	1.42 (0.97–2.09)
One	2.31 (1.71–3.12)	2.70 (2.04–3.58)	3.16 (2.15–4.65)	2.46 (1.96–3.08)	3.09 (2.50–3.82)	3.88 (2.93–5.16)
Two	3.49 (2.46–4.95)	4.59 (3.33–6.33)	6.04 (3.70–9.87)	6.77 (5.33–8.62)	7.96 (6.34–9.98)	9.35 (6.72–13.00)

Data are HR (95% CI). *Adjusted for age at baseline, study center, and sex. †Abnormal metabolic traits included obesity, low HDL cholesterol.

appendix Fig. 1; online appendix Table 2). When each effect measure modifier was studied separately, a larger ICR for obesity ($P = 0.02$) in Caucasians and a larger ICR for low HDL cholesterol ($P = 0.004$) in African Americans were observed (Table 3), but testing by bootstrapping (25) did not support significant racial differences (online appendix A).

DISCUSSION

TCF7L2 has been implicated as an important type 2 diabetes susceptibility gene in different populations. Our study replicates the association between the T-allele at rs7903146 and type 2 diabetes risk in Caucasians and provides the first significant evidence of association in a large population-based study of an African American population (4–6,8,). The rs7903146 polymorphism was significantly associated with type 2 diabetes risk in two other African-ancestry studies (4,6), but none of these two studies were population based. Our study also contributes new evidence for additive interaction between *TCF7L2* variants and obesity ($P = 0.02$) in Caucasians and HDL cholesterol ($P = 0.004$) in African Americans (Table 3). Indeed, we demonstrate that the risk of developing type 2 diabetes associated with this *TCF7L2* variant is substantially increased in the context of some of these well-known metabolic risk factors for type 2 diabetes.

When studied separately, the most prominent additive interaction with genotype, indicated by larger ICRs, was for low HDL in African Americans and obesity in Caucasians (Table 3). To our knowledge, no interaction has been reported between low HDL and rs7903146. A multiplicative interaction with obesity and high BMI was observed in two previous studies (8,10). Both studies found that the risk of type 2 diabetes increased in lean individuals, whereas no significant association was noted in obese or overweight individuals, suggesting that the SNP rs7903146 is a much more influential risk factor for lean individuals than for obese individuals. However, in our study the effect in obese Caucasians appears slightly stronger than the effect in lean Caucasians (HR for CT vs. CC 1.25 [1.08–1.45] in obese individuals and 1.20 [1.05–1.36] in nonobese individuals), which is discrepant from the findings of previous studies. The differences in study populations (Caucasian vs. Japanese and men/women vs. men only), analysis methods (additive vs. multiplicative interactions), study designs (cohort vs. case/control and different inclusion/exclusion criteria) may explain these study discrepancies. Moreover, the mechanism of action of *TCF7L2* variants in the context of obesity or other metabolic impairments needs to be studied further.

The majority of current literature suggests that *TCF7L2* is associated with impaired insulin secretion but not with increased insulin resistance (5,26,27). We found a slightly lower fasting insulin and HOMA-IR concentration among individuals with the T-(risk) allele, suggestive of impaired insulin secretion. A possible explanation of our study findings is that *TCF7L2* may impair β-cell function, which, when combined with insulin resistance caused by other factors, provides a double hit that disproportionately increases the risk for type 2 diabetes. Our study demonstrates that the risk of type 2 diabetes was substantially increased among rs7903146 T-allele carriers with obesity and low HDL cholesterol in comparison with those CC individuals with HDL in the normal range who were lean (online appendix Table 2). There is strong evidence that abnormal metabolic traits including obesity and dyslipidemia aggregate in type 2 diabetic patients and their relatives (28,29). Genetic factors interacting with shared and unique environmental factors may cause this aggregation of metabolic traits (28). Although our study has implicated, for the first time, interesting relationships between these metabolic risk factors, the *TCF7L2* variants, and type 2 diabetes, the mechanism of action of *TCF7L2* variants on type 2 diabetes remains to be determined.

In conclusion, our study provides important new evidence for an association between *TCF7L2* and type 2 diabetes in a large African American population. We also provide estimates of the predicted cumulative incidence of type 2 diabetes over 9 years of follow-up associated with this genetic variant in the context of metabolic impairments that usually precede and coexist with type 2 diabetes. Our study findings need to be replicated in other population-based studies, and further study is needed on the mechanisms by which the *TCF7L2* gene acts in the context of metabolic traits in the pathogenesis of type 2 diabetes.

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