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Diabetes Metab Res Rev. Author manuscript; available in PMC 2011 July 1.

Published in final edited form as:
Diabetes Metab Res Rev. 2010 July ; 26(5): 371–377. doi:10.1002/dmrr.1087.

Transcription Factor 7-Like 2 (*TCF7L2*) Polymorphism and Context-Specific Risk of Impaired Fasting Glucose in African American and Caucasian Adults: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Although variants in the transcription factor 7-like 2 (*TCF7L2*) gene are consistently associated with impaired fasting glucose (IFG) in Caucasians, data from large population-based studies of African Americans are lacking. Moreover, few studies have investigated the effects of *TCF7L2* on IFG in the context of metabolic risk factors for diabetes.

Methods—We investigated the association between the *TCF7L2* rs7903146 polymorphism and incident IFG defined as fasting serum glucose levels of 100–125 mg/dl (5.6–6.9 mmol/l) in 1,377 African American and 5,152 Caucasian participants without diabetes and IFG at intake who participated in the Atherosclerosis Risk in Communities (ARIC) Study in 1987–1989 and were followed for 9 years.

Results—Incident IFG was identified in 810 (58.8%) African American and 2,652 (51.5%) Caucasian participants. Compared to homozygous CC Caucasian individuals, heterozygous CT [hazard ratio (HR) = 1.09 (95% CI=1.03–1.15)] and homozygous TT [1.18 (1.05–1.33)] individuals had significantly higher risk of developing IFG over 9-year follow up. The association between rs7903146 and IFG risk was stronger in Caucasians with obesity [$HR_{CT\ vs.\ CC}$=1.28 (1.12, 1.47); $HR_{TT\ vs.\ CC}$=1.65 (1.25, 2.17)] or high triglycerides [$HR_{CT\ vs.\ CC}$=1.31(1.10, 1.56); $HR_{TT\ vs.\ CC}$=1.72 (1.21, 2.43)]. No association of the *TCF7L2* rs7903146 polymorphism and incident IFG was noted in African Americans.

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Conclusions—Our study replicates the association between rs7903146 and IFG risk in a population-based, longitudinal cohort of Caucasians but not in African Americans. For the first time, our study provides evidence for interactions between *TCF7L2* and metabolic risk factors on the occurrence of IFG in Caucasians.

Keywords

Gene-environment interaction; Impaired fasting glucose; Transcription factor 7-like 2 (*TCF7L2*)

INTRODUCTION

Impaired fasting glucose (IFG), an intermediate stage between normoglycemia and diabetes, is characterized by defects in insulin sensitivity and early-phase insulin secretion [1,2]. The transcription factor 7-like 2 (*TCF7L2*) gene, a Wingless and Int (Wnt) signaling-associated transcription factor located on chromosome 10q25, has emerged as a consistently replicated susceptibility gene for type 2 diabetes and IFG [3,4,5,6,7]. In our previous work, we demonstrated a significant association between the T allele at single nucleotide polymorphism (SNP) rs7903146 and the risk of incident type 2 diabetes in middle-aged African American and Caucasian participants of the Atherosclerosis Risk in Communities (ARIC) Study[8]. The rs7903146 T allele has been described either as the causal risk variant or the closest correlate to an unidentified functional variant [9], possibly impairing the glucagon-like peptide-1-induced insulin secretion[10], but the exact mechanism is still under investigation.

Although an effect of *TCF7L2* on IFG has been observed in Caucasians [6,7], no studies of TCF7L2 and prediabetes as quantified by incident IFG have been conducted in African Americans. Moreover, potential *TCF7L2* gene–metabolic risk factors interactions on IFG have been largely unexplored.

Our previous work focused on the association between the rs7903146 SNP and type 2 diabetes[8]. In this study, we investigated whether the rs7903146 SNP of the *TCF7L2* gene is associated with incident IFG in a large community-based cohort of African-American and Caucasian middle-aged adults in the ARIC Study. A second objective is to evaluate whether the effect of the rs7903146 SNP on IFG varies by obesity and triglyceride levels.

MATERIALS 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 to 64 years old at baseline (1987–1989), selected from 4 US communities: Forsyth County, NC; Jackson, MS; the northwestern suburbs of Minneapolis, MN; and Washington County, MD. By design, African-Americans were over-sampled at the Forsyth County site and were exclusively sampled in Jackson and thus constituted 27% of the baseline cohort. Participants received an extensive examination, including medical, social, and demographic data, and were reexamined every three years with the first screen (baseline) occurring in 1987–89, the second in 1990–92, the third in 1993–95, and the fourth and last exam in 1996–98. 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 at baseline or incident diabetes during follow-up (n=3,379), participants with prevalent IFG at baseline (n=4,472), participants with missing genotype data or who

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did not provide consent for the use of their DNA (*n*=525), and participants with missing information on incident IFG (*n*=784). Diabetes was defined as fasting serum glucose levels of at least 7.0 mmol/L (126 mg/dl), nonfasting glucose levels of at least 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 [2]. After these exclusions, 6,529 baseline examination participants (1,377 African American and 5,152 Caucasians) were available for analysis. The institutional review boards at all participating institutions approved the procedures and all participants included in the analysis gave informed consent.

All covariates were measured at the baseline exam (visit 1). As a measure of prediabetes, individuals with fasting serum glucose levels of 100–125 mg/dl (5.6–6.9 mmol/l)[2] were classified as having IFG. Individuals without IFG at baseline who subsequently met this criterion for incident IFG at visit 2, 3, or 4 were considered to be incident cases in the analysis.

Self-reported cigarette smoking exposure was defined as ever smoking versus never smoking obtained by a personal interview. Body mass index (BMI) was calculated as measured weight (kg) divided by the square of measured height (m^2). Individuals with a BMI ≥30 kg/m^2 were classified as obese[12]. Elevated waist circumference (WC) was defined as WC≥102cm in males or WC≥88cm in females[13]. Blood pressure 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 ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg or a history of anti-hypertension medication use[14]. Glucose was assessed by a modified hexokinase/glucose-6-phosphate dehydrogenase procedure[15]. Plasma total cholesterol levels, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured by enzymatic methods. Low HDL-C was defined as less than 40 mg/dl in males and 50 mg/dl in females. High triglyceride was defined as triglyceride levels higher than 200 mg/dl[16]. Insulin was measured by radioimmunoassay (^{125}Insulin kit; Cambridge Medical Diagnosis, Bilerica, MA). Physical activity was quantified using a slightly modified version of the Baecke physical activity questionnaire[17], that classified work, sport and leisure activities into categories ranging from 1 (low) to 5 (high).

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 IDT (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 between blind duplicates was 98% and the simple Kappa coefficient was 0.97 indicating 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 IFG over a 9-year follow-up under a semiparametric regression model. We used Cox proportional hazards to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of incident IFG. The hazard function was formulated on the age scale and date of onset of IFG was interpolated using blood glucose levels at the visits at each end of the triennial intervals[18]. Furthermore, we assessed the association between IFG and *TCF7L2* using a more stringent definition of IFG, categorizing individuals with a fasting

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glucose value of 110 – 125 mg/dl as affected. Lastly, we evaluated the association between rs7903146 and repeated fasting glucose values over 9 years of follow-up (visit 1–4) in the ARIC study population using Generalized Estimating Equation models.

Covariates including history of ever smoking, BMI, obesity, hypertension, plasma HDL-C, lipid medications, and history of work, sport, leisure time physical activity level were assessed as potential confounders. We employed the change-in-estimate procedure[19] to select confounders with a ≥10% change in the estimated HR required for retention in the model. As all covariates assessed did not modify, or only slightly modified the estimated effect of exposure, they were all removed from further analyses.

Following the published literature [4] and our findings from previous research [8], we compared heterozygous CT-genotype and homozygous TT-genotype individuals to CC-genotype individuals, using the rs7903146 CC-genotype as the referent group, and the T allele as the risk variant. A variable taking on the values 0 for genotype CC, 1 for genotype CT, and 2 for genotype TT was used to test for additive genetic effects.

Gene–environment interaction testing was assessed on the multiplicative and additive scales between genotypes and different metabolic risk factors including obesity, elevated waist circumference, hypertension, high triglycerides, and low HDL-C. With regard to multiplicative interaction, variables were considered to be potential effect measure modifiers if they departed from multiplicativity assessed by the Wald χ^2 test for significance of the estimated β-coefficient for the interaction term [20]. For additive interaction, variables were considered as potential modifiers if departure from additivity was detected by the interaction contrast ratio (ICR) [20,21]. 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[20]. Thus, ICR refers to the increased risk due to an additive interaction between the metabolic risk factors and the T risk allele adjusted for age, gender, and study center. Assuming an additive mode of inheritance, the ICR comparing TT to CT is equal to the ICR comparing CT to CC when 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 IFG. The HR and the variance covariance matrix were used to calculate ICR values and their 95% confidence intervals[21]. A p value <0.05 was considered to indicate an important modifier for both multiplicative and additive interaction assessments, despite the multiple tests as interaction tests tend to be underpowered [22].

Power analyses were performed using QUANTO 1.2 assuming unmatched case-control study design [23]. Analysis was performed separately for Caucasians and African-Americans, under an additive model and a two-sided p value of 0.05. We estimated 60% and 20% power to detect an odds ratio of 1.10 (CT vs. CC) in Caucasian and African-Americans, respectively; for an odds ratio of 1.15, the power was estimated as 90% and 40%, respectively. However, because we estimated hazard ratios in the study and not odds ratios, these power estimates were likely conservative.

RESULTS

The allele frequencies for rs7903146 in both races were in Hardy–Weinberg equilibrium (p>0.05). Selected baseline characteristics of the ARIC Study participants by race and genotype status are presented in Table 1. At the baseline exam, no significant differences in demographic or behavioral characteristics (age, gender, leisure physical activity level, and smoking) were noted by genotype status in Caucasian and African American ARIC

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participants. Moreover, no significant differences in hypertension, glucose, insulin, obesity relate traits, triglycerides, and HDL-C were noted.

Over the course of 9 years of follow-up, incident IFG was identified in 810 (58.8%) African American and 2,652 (51.5%) Caucasian ARIC participants (Table 2). The rs7903146 T allele was observed with similar frequency in African-American and Caucasian individuals, but was more common among incident IFG cases compared with non-cases in Caucasians (Table 2). The rs7903146 T allele was significantly associated with incident IFG in Caucasian participants [$HR_{CT\ vs.\ CC}$ (95% CIs)=1.09 (1.03, 1.15); $HR_{TT\ vs.\ CC}$(95% CIs)=1.18 (1.05, 1.33)], but not in African American participants [$HR_{CT\ vs.\ CC}$ (95% CIs)=0.99 (0.89, 1.10); $HR_{TT\ vs.\ CC}$ (95% CIs)=0.98 (0.79, 1.22)] (Table 2).

To interrogate the consistency of our findings, we assessed the association between IFG and *TCF7L2* using a more stringent definition of IFG (110 – 125 mg/dl) and similar results were obtained (data not shown). Lastly, a significant association between the rs7903146 T allele and repeated fasting glucose across visit 1–4 was noted in Caucasians (β=0.2480 with p=0.0389) but not in African Americans (β=0.3002 with p=0.2826), which is consistent with the IFG findings.

We identified obesity and high triglyceride as important effect measure modifiers in Caucasians, but no important modifiers were noted in African Americans (Table 3; Figure 1; Online Appendix Table 1). Specifically, among non-obese Caucasians, heterozygous CT [HR=1.07 (95% CI=1.00, 1.14)] and homozygous TT [1.14 (1.00, 1.30)] individuals had slightly higher HRs (95%CI) of IFG over 9 years of follow-up compared to homozygous CC individuals, whereas among obese Caucasians, heterozygous CT [1.28 (1.12, 1.47)] and homozygous TT [1.65 (1.25, 2.17)] individuals had significantly higher HRs (95%CI) of IFG compared to CC individuals (Figure 1; multiplicative interaction p value=0.01). Similar results were obtained for high triglycerides. When each effect measure modifier was studied separately, we observed a slightly larger ICR for obesity in Caucasians (Table 3), but testing by bootstrapping did not find significant differences between ICRs for obesity and high triglycerides[24].

DISCUSSION

TCF7L2 has been implicated as an important IFG susceptibility gene in different Caucasian populations [6,7]. To our knowledge, our study is the first population-based study on the *TCF7L2* rs7903146 and prediabetes as measured by incident IFG in African Americans and no association was noted. An earlier study in non-diabetic African American women (n=118 with 11 prevalent IFG cases) reported the lack of an association with prevalent IFG (effect estimates not reported) [25], which is consistent with our findings. Our study replicates the association between the T allele at rs7903146 and IFG risk in Caucasians, and for the first time contributes evidence for interactions between *TCF7L2* variants and obesity and high triglycerides in Caucasians. Indeed, we demonstrate that the risk of developing IFG associated with this *TCF7L2* variant is substantially increased in the context of well known metabolic risk factors for type 2 diabetes.

We and other investigators have previously demonstrated an association between the *TCF7L2* rs7903146 and type 2 diabetes in both races [3,4,8]. In this study, an association with IFG was noted in Caucasians only. The majority of current literature suggests that *TCF7L2* is associated with impaired insulin secretion, but not with increased insulin resistance [5,26,27]. In our previous study on *TCF7L2* and type 2 diabetes in ARIC[8], we found a slightly lower fasting insulin and homeostasis model assessment (HOMA) – insulin resistance concentration among individuals with the T risk allele, suggestive of impaired

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insulin secretion. A possible explanation of our study findings is that *TCF7L2* may impair beta cell function, which when combined with insulin resistance caused by other factors such as obesity provides a "double hit" that disproportionately increases the risk for IFG and then type 2 diabetes. Given the number of analyses performed in this study, we applied a crude Bonferroni correction (five potential effect measure modifiers and the full sample, N=6), noting that such an approach is an over-correction because many of the analytic runs assessed the same dependent variable. If such a correction were applied, the study results for the additive interactions with obesity and high triglycerides remain statistically significant although the association between *TCF7L2* rs7903146 and IFG became non-significant, which actually highlights the importance of our interaction analysis. Our study sample is a group with fairly modest hyperglycaemia during 9 years of follow-up. The gradual rise in fasting glucose with age may explain the modest effect observed between rs7903146 and IFG, but the interactions with obesity and high triglycerides has beyond that (Table 3), which highlights the importance of evaluating gene-metabolic risk factor interaction.

We observed an association between *TCF7L2* rs7903146 and type 2 diabetes in our African American sample[8], but did not observe an association with IFG in this study. The lack of association within the African American may suggest that *TCF7L2* rs7903146 primarily impair the glucose metabolism through impaired glucose tolerance (IGT), which needs to be tested by 2-hour postprandial glucose data. Unfortunately the ARIC Study does not have sufficient data on 2-hour glucose (i.e. the data was only available at visit 4 and had very low power to detect a modest effect). The lack of association may also reflect confounding by unmeasured covariates that are differentially distributed in African American and Caucasian participants, both of which warrant further investigation. Third, it is worth noting that the limited power to detect such a modest effect in the African American sample (calculated as 20% for a relative risk of 1.10) may explain our findings as well.

Our data identified obesity and high triglycerides as significant effect measure modifiers in Caucasians. When studied separately, the most prominent interaction with genotype was for obesity (Table 3, Figure 1). To our knowledge, no interaction has been reported between high triglycerides and rs7903146. A multiplicative interaction with obesity/high BMI on the outcome of type 2 diabetes was observed in two previous studies by other investigators [28,29]. Both studies found that the risk of type 2 diabetes increased in lean individuals whereas no significant association was noted in obese/over-weight individuals, suggesting that the SNP rs7903146 is a much more influential risk factor for lean individuals than for obese individuals. However, in this current study and our previous publication in diabetes [8], the effect in obese Caucasians appears slightly stronger than the effect in lean Caucasians, which is discrepant from previous studies.

The differences in study populations (Caucasians vs. Japanese, men/women vs. men only), analysis methods (additive vs. multiplicative interactions), study designs (cohort vs. case-control, different inclusion/exclusion criteria) may explain these study discrepancies. Although we are unable to elucidate the pathogenesis underlying the observed statistical interactions, strong evidence indicates that abnormal metabolic traits including obesity and dyslipidemia aggregate in diabetic patients and their relatives [30,31]. Genetic factors interacting with shared and unique environmental factors may cause this aggregation of metabolic traits [30]. Although our study has implicated, for the first time, interesting relationships between these metabolic risk factors, the *TCF7L2* variants and IFG in Caucasians, the role of *TCF7L2* variants in pathogenesis of IFG in the context of metabolic risk factors remains to be determined.

Our study findings have public health significance of potential importance since they suggest that having one or two rs7903146 T risk alleles only partially informs one's risk for

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prediabetes, as quantified by IFG. In the Caucasian population, the risk of IFG conferred by the T risk allele of rs7903146, even in the context of metabolic risk factors, only demonstrated a modest risk. In the African American population, no association between the T risk allele and IFG was noted. Thus, the cumulative risk of IFG likely depends on multiple susceptibility variants, the gene-gene interactions, and most importantly, “established” risk factors for type 2 diabetes such as BMI and other lifestyle habits.

In conclusion, our study replicates the association between the T allele at rs7903146 and IFG risk in Caucasians, whereas no associations were observed in African Americans. Our study provides new evidence for interactions between *TCF7L2* and metabolic risk factors on the risk of IFG in Caucasians, as was previously demonstrated for type 2 diabetes. The reported differences between African American and Caucasian subpopulations require replication in larger epidemiological studies, as we were underpowered to detect the very modest effects that were observed in the Caucasians.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

ACKNOWLEDGEMENTS / DISCLOSURE

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022.

C.J.G. is an employee and shareholder of Merck & Co., Inc.

We are indebted to the staff and participants in the Atherosclerosis Risk in Communities Study for their important contributions.

This work has been published in abstract form [Genetic Epidemiology 2008; 32: 7(721)].

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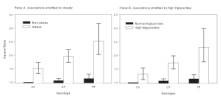

Figure 1.

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Table 1

Selected characteristics of the Atherosclerosis Risk in Communities Study participants at baseline, by race and genotype status.

	African American				Caucasian			
	CC	**CT**	**TT**	***p***	**CC**	**CT**	**TT**	***p***
n	695	569	113		2679	2084	389	
Age (years)	52 ± 6	52 ± 6	53 ± 6	0.76	54 ± 6	54 ± 6	53 ± 6	0.06
Sex (male)	241 (34.68)	210 (36.91)	36 (31.86)	0.52	1010 (37.70)	807 (38.72)	146 (37.53)	0.75
Ever Smoked	344 (49.50)	292 (51.32)	53 (46.90)	0.64	1499 (56.00)	1163 (55.83)	213 (54.76)	0.90
Leisure-time Physical Activity [a]	2.12 ± 0.59	2.16 ± 0.59	2.11 ± 0.56	0.42	2.5 ± 0.54	2.5 ± 0.53	2.53 ± 0.52	0.53
Obese[b]	214 (30.79)	155 (27.29)	31 (27.43)	0.37	412 (15.38)	273 (13.12)	49 (12.6)	0.06
BMI (kg/m^2)	28.37 ± 5.89	27.99 ± 5.23	27.70 ± 5.02	0.32	25.83 ± 4.29	25.55 ± 4.16	25.64 ± 4.23	0.07
Elevated WC[c]	366 (52.66)	276 (48.59)	56 (49.56)	0.35	1142 (42.63)	842 (40.40)	161 (41.39)	0.30
WC (cm)	95.13 ± 14.70	94.05 ± 13.10	93.12 ± 13.03	0.21	92.55 ± 12.41	91.76 ± 11.87	92.03 ± 11.91	0.08
Hypertension[d]	302 (43.64)	238 (42.05)	47 (41.59)	0.82	529 (19.86)	376 (18.13)	61 (15.72)	0.08
Glucose (mg/dl)[e]	91.33 ± 5.77	91.58 ± 5.34	91.60 ± 5.39	0.70	92.40 ± 4.88	92.46 ± 4.82	92.13 ± 4.90	0.47
Insulin (μU/ml)[e]	11.12 ± 7.75	10.45 ± 6.82	10.19 ± 6.51	0.18	8.23 ± 5.40	7.88 ± 5.13	7.89 ± 4.87	0.06
High triglyceride[f]	24 (3.55)	20 (3.60)	3 (2.70)	0.97	245 (9.16)	198 (9.52)	36 (9.28)	0.91
Triglycerides (mg/dl)	95.32 ± 52.14	95.25 ± 52.75	91.05 ± 50.34	0.71	118.64 ± 67.09	117.94 ± 72.40	121.85 ± 84.62	0.61
Low HDL-C[g]	174 (25.74)	139 (25.05)	22 (19.82)	0.42	883 (33.02)	651 (31.30)	132 (34.02)	0.35
HDL-C (mg/dl)	58.85 ± 18.26	58.88 ± 18.61	61.18 ± 19.00	0.45	54.26 ± 17.21	54.83 ± 17.44	53.91 ± 17.17	0.43

Data are means ± SD or *n* (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; HDL-C, high density lipoprotein cholesterol; WC, waist circumference.

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[a] Leisure time physical activity was derived from four questions regarding the frequency of television watching, walking, bicycling during the leisure time, and walking and/or bicycling to/from work, and was measured on a 5-point scale, with 1 indicating the lowest level of activity and 5 the highest[32];

[b] obesity was defined as BMI ≥30 kg/m^2;

[c] elevated WC was defined as WC≥102cm in males or WC≥88cm in females;

[d] hypertension was defined as systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg or a history of anti-hypertension medication use;

[e] prevalent diabetes and IFG cases were excluded;

[f] high triglyceride was defined as triglyceride levels higher than 200 mg/dl;

[g] low HDL-C was defined as less than 40 mg/dl in males and 50 mg/dl in females.

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Table 2

Genotypic frequency of *TCF7L2* rs7903146 by race and incident IFG status, cumulative incidence of IFG by race and genotype over 9 years of follow-up, and estimated hazard ratio of rs7903146 on IFG by race: The ARIC Study.

	African American				Caucasian			
	Non-Cases/Cases	**Cumulative Incidence (%) (95%CI)**	**HR (95% CI)[a]**	***p*[b]**	**Non-Cases/Cases**	**Cumulative Incidence (%) (95%CI)**	**HR (95% CI)[a]**	***p*[b]**
n	567/810	63.73 (60.64, 66.58)			2500/2652	53.87 (52.37, 55.31)		
CC	291(51)/404(50)	63.78 (59.84, 67.34)	1.00		1354(54)/1325(50)	52.19 (50.26, 54.04)	1.00	
CT	221(39)/348(43)	63.64 (60.05, 66.91)	0.99 (0.89, 1.10)	0.86	966(39)/1118(42)	55.19 (53.42, 56.89)	1.09 (1.03, 1.15)	0.01
TT	55(10)/58(7)	63.50 (56.49, 69.38)	0.98 (0.79, 1.22)		180(7)/209(8)	58.24 (54.66, 61.53)	1.18 (1.05, 1.33)	
T allele (%)	29/29				27/29			

Abbreviation: CI, confidence interval; HR, hazard ratio; IFG, impaired fasting glucose.

[a] Adjusted for age at baseline, study center and gender;

[b] *p* value for HR.

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Table 3

Association of *TCF7L2* rs7903146 with IFG [HR (95% CI)] modified by obesity and high triglycerides, respectively, over 9 years of follow-up in ARIC

Characteristics	CC genotype		CT genotype		TT genotype		Multiplicative Interaction	Additive Interaction
	N	HR (95% CI)[a]	N	HR (95% CI)[a]	N	HR (95% CI)[a]	p^b	ICR (p^c)
African-American								
Obesity[d]								
No	481	1	413	1.03 (0.90, 1.17)	82	1.06 (0.82, 1.38)	0.40	−0.12 (0.42)
Yes	214	1.40 (1.15, 1.71)	155	1.31 (1.08, 1.59)	31	1.22 (0.87, 1.70)		
High triglycerides[e]								
No	652	1	535	1.00 (0.90, 1.12)	108	1.01 (0.80, 1.26)	0.32	0.44 (0.30)
Yes	24	1.18 (0.71, 1.97)	20	1.63 (1.05, 2.51)	3	2.23 (0.90, 5.56)		
Caucasian								
Obesity[d]								
No	2267	1	1808	1.07 (1.00, 1.14)	340	1.14 (1.00, 1.30)	0.01	0.38 (0.007)
Yes	412	1.52 (1.33, 1.73)	273	1.96 (1.74, 2.21)	49	2.53 (2.03, 3.17)		
High triglycerides[e]								
No	2429	1	1882	1.07 (1.00, 1.14)	352	1.14 (1.00, 1.29)	0.02	0.36 (0.002)
Yes	245	1.31 (1.11, 1.54)	198	1.73 (1.51, 1.99)	36	2.30 (1.76, 3.00)		

Abbreviation: ICR, interaction contrast ratio; IFG, impaired fasting glucose; CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age at baseline, study center and gender;

[b] p value for the Wald χ^2 test;

[c] p value for ICR;

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[d] obesity was defined as BMI ≥30 kg/m^2;

[e] high triglyceride was defined as triglyceride levels higher than 200 mg/dl.