Published in final edited form as:
Diabetologia. 2008 June ; 51(6): 968–970. doi:10.1007/s00125-008-1004-1.

TCF7L2 SNPs, cardiovascular disease, and all-cause mortality: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Aims and Hypothesis—We hypothesize that transcription factor 7-like 2 (*TCF7L2*) single nucleotide polymorphisms (SNPs) are associated with cardiovascular disease (CVD) and that the associations differ in diabetic and non-diabetic participants.

Methods—Black and white subjects from the Atherosclerosis Risk in Communities (ARIC) study who were free of prevalent CVD at baseline and genotyped for rs7903146, rs12255372, rs7901695, rs11196205, and rs7895340 were included in this analysis (n = 13,369). Cox proportional hazard regression was used to estimate the associations of polymorphisms and incident events and logistic and linear regression were used for associations with baseline risk factor levels.

Results—*TCF7L2 SNPs* were not significantly associated with incident coronary heart disease, ischemic stroke, CVD, prevalent peripheral artery disease (PAD), or with all-cause mortality in the full cohort or stratified by race.

Conclusions/Interpretation—In the whole cohort, *TCF7L2* SNPs were not associated with incident CVD, all-cause mortality, or prevalent PAD. This result suggests that the increased health risk associated with rs7903146 genotype is specific to diabetes.

Keywords

All-cause mortality; Cardiovascular disease; Coronary heart disease; Diabetes; Peripheral artery disease; Stroke; Transcription factor 7-like 2 (*TCF7L2*)

Introduction

Diabetes is a major risk factor for stroke, peripheral artery disease (PAD), and coronary heart disease (CHD). Transcription factor 7-like 2 (*TCF7L2*) polymorphisms have been associated with diabetes in numerous studies[1–3] and the magnitude of risk conferred by *TCF7L2* variants is greater that for any previously described common variant. The single nucleotide polymorphism (SNP) rs7903146 is the most highly associated of the known variants and is associated with a 40% increased risk of diabetes per allele[4]. The gene *TCF7L2* is located on chromosome 10 and encodes the transcription factor Tcf-4. Of

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Duality of Interest: None of the authors has a conflict of interest to declare.

particular interest, a specific role for Tcf-4 has been shown in the process of vascular remodeling. Moreover, transcriptional activation of Tcf-4 turns on the NF-kB signaling pathway, which regulates inflammatory signaling pathways[5]. Data from the MONICA/KORA Surveys showed the T allele of rs7903146 was inversely associated with homeostasis model assessment of percent β-cell function (HOMA-%B) and fasting insulin suggesting a role in pancreatic beta cell function[3]. Support for this hypothesis is seen in cell culture experiments and other human studies. Depleting islet cells of *TCF7L2* in culture resulted in significant increases in beta-cell apoptosis and decreases in proliferation and glucose stimulated insulin secretion[6]. Therefore, we hypothesize that *TCF7L2* SNPs would be associated with cardiovascular disease (CVD) in the Atherosclerosis Risk in Communities (ARIC) Study. Furthermore, we investigated whether the associations of *TCF7L2* genotypes with CVD differ in diabetic and non-diabetic participants.

Subjects, materials, and methods

The ARIC study is a prospective cohort study of 15,792 participants investigating the etiology of atherosclerosis and described in detail elsewhere[7]. For this analysis, individuals were excluded based on the following criteria; race other than black or white (n=48), blacks from centers with small numbers (n=55), prevalent CHD (n=763), missing data for prevalent CHD (n=339), prevalent stroke (n=264), and missing genotype data for *TCF7L2* SNP rs7903146 (n=954). The final analysis sample included 13,369 subjects. For the investigation with PAD, individuals missing ankle brachial index were further excluded (n=457). Ascertainment and standardized case definitions for PAD[8], CHD[9], stroke[10], carotid intimal medial thickness (IMT)[11], mortality[12], and diabetes[13] have been described elsewhere. Five *TCF7L2* SNPs were genotyped on stored DNA using the TaqMan® System; rs7903146, rs12255372, rs7901695, rs11196205, and rs7895340 (www.appliedbiosystems.com.). Five percent of samples were re-genotyped for quality control and 726 ARIC participants were genotyped in duplicate. The percentage of agreement was 96% and simple Kappa coefficient was 0.93 indicating good genotype quality. All data were analyzed with SAS, Version 9 (SAS Institute Inc., Cary, NC). We tested for Hardy Weinberg equilibrium using the χ^2 goodness of fit test. Cox proportional hazard regression was used to estimate the associations of SNPs and incident events and logistic and linear regression were used for baseline prevalence measures. We had 80% power to detect a relative risk of 1.17 for incident CHD with an alpha = 0.05.

Results

The study population included 27% blacks, 57% were female, and the mean age was 54 years. All 5 SNP genotype frequencies were in Hardy-Weinberg equilibrium. The following results focus on rs7903146. Baseline diabetes, current smoking, life-time smoking exposure (pack-years), and BMI (kg/m^2) differed by genotype. For the CC, CT and TT genotypes respectively, the baseline prevalence of diabetes was 9.4%, 12.2%, and 14.2% ($p<0.0001$) and the percentage of current smokers was 25%, 26%, and 28% ($p=0.03$). The T-allele was associated with lower mean BMI (CC=27.8, CT=27.5, TT=27.4 kg/m^2, $p=0.03$) and more pack-years of smoking (CC=14.7, CT=15.2, and TT=16.3, $p=0.05$). There was no difference by genotype for age, race, sex, current drinking, ethanol intake, waist-to-hip ratio, total cholesterol, HDL and LDL cholesterol, triglycerides, or systolic and diastolic blood pressure.

The T-allele of rs7903146 was not significantly associated with incident CHD, ischemic stroke, or CVD, or with all-cause mortality in the full cohort or stratified by race (Table 1). In whites with prevalent diabetes, the T-allele was associated with incident CHD but only in

the model adjusted for age, sex, BMI, and smoking status (HR = 1.21, p = 0.04). We found no significant association of this allele with prevalent PAD or IMT (data not shown).

Discussion

We hypothesized that *TCF7L2* SNPs would be associated with increased risk of CVD and all-cause mortality given the association of these variants with diabetes. In the whole cohort, rs7903146 was not associated with incident CVD, all-cause mortality, or prevalent PAD. The T-allele of rs7903146 was associated with smoking and inversely associated with BMI in the whole cohort and in a subset of whites with prevalent diabetes this allele was associated with incident CHD. Results from the Go-Darts Study of over 6,500 European subjects reported the T-allele was associated with increased hemoglobin A1c (HbA1c) in both cases and controls. These researchers also reported that the T-allele was overrepresented in individuals requiring insulin treatment and underrepresented in patients managed by diet alone suggesting that variants of *TCF7L2* may be associated with disease severity and therapeutic efficacy[14]. Therefore, a reasonable hypothesis is that the small increased risk of CHD seen in our study may be the result of suboptimal or ineffective treatment of diabetes in the earlier onset cases. However, the increased risk observed in the white subgroup was not seen in the corresponding black group (HR = 1.04, 95% CI = 0.79–1.36). While the association may be spurious given that this was one of several subgroup analyses, the inconsistency between races may result from the smaller sample size in this racial group. In prevalent diabetics, we had 80% power to detect a relative risk of 1.54 and 1.78 for incident CHD in whites and blacks respectively. Clearly, replication in a larger and possibly younger diabetic population is needed to confirm or refute this finding.

In their entirely, these results suggest that while there may be a slight increased risk of CHD in early onset diabetes cases, the increased health risk associated with rs7903146 genotype is specific to diabetes.

Acknowledgments

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. The authors thank the staff and participants of the ARIC study for their important contributions.

Abbreviations

ARIC	Atherosclerosis Risk in Communities
CHD	coronary heart disease
CVD	cardiovascular disease
HbA1c	hemoglobin A1c
HOMA-%B	homeostasis model assessment of percent β-cell function
IMT	intimal medial thickness
PAD	prevalent peripheral artery disease
SNPs	single nucleotide polymorphisms
TCF7L2	transcription factor 7-like 2

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Diabetologia. Author manuscript; available in PMC 2009 June 01.

Table 1

Numbers of Events (n) and Hazard Ratios (95% confidence intervals) of incident CVD and all-cause mortality per T-Allele of rs7903146, ARIC 1987–2004

	Blacks		Whites		All	
	Minimally-Adjusted	**Fully-Adjusted**	**Minimally-Adjusted**	**Fully-Adjusted**	**Minimally-Adjusted**	**Fully-Adjusted**
CHD	(n=389) 1.12 (0.96–1.3)	(n=374) 1.09 (0.93–1.28)	(n=1338) 1.01 (0.93–1.10)	(n=1326) 1.01 (0.93–1.09)	(n=1727) 1.04 (0.96–1.11)	(n=1700) 1.02 (0.95–1.1)
CHD, prevalent-diabetes	(n=122) 1.11 (0.85–1.45)	(n=119) 1.04 (0.79–1.36)	(n=263) 1.19 (0.99–1.4)	(n=260) 1.21 (1.01–1.44)	(n=385) 1.16 (1.0–1.35)	(n=379) 1.14 (0.98–1.33)
CHD, no-diabetes	(n=202) 1.06 (0.86–1.32)	(n=195) 1.07 (0.86–1.33)	(n=925) 0.93 (0.84–1.03)	(n=917) 0.92 (0.83–1.02)	(n=1127) 0.95 (0.87–1.04)	(n=1112) 0.94 (0.86–1.04)
Ischemic Stroke	(n=235) 1.12 (0.92–1.36)	(n=221) 1.14 (0.93–1.40)	(n=314) 0.99 (0.83–1.17)	(n=311) 0.97 (0.82–1.16)	(n=549) 1.04 (0.91–1.18)	(n=532) 1.04 (0.91–1.18)
CVD	(n=594) 1.10 (0.98–1.25)	(n=567) 1.10 (0.98–1.25)	(n=1594) 1.0 (0.93–1.08)	(n=1578) 0.99 (0.92–1.07)	(n=2188) 1.03 (0.96–1.10)	(n=2145) 1.02 (0.95–1.08)
All-cause mortality	(n=757) 1.01 (0.91–1.13)	(n=726) 0.99 (0.89–1.11)	(n=1354) 1.03 (0.95–1.12)	(n=1331) 1.00 (0.92–1.08)	(n=2111) 1.03 (0.96–1.09)	(n=2057) 1.00 (0.93–1.07)

Minimally Adjusted = age and sex; race in the combined analysis

Fully-adjusted = minimally adjusted variables + BMI, smoking status, pack-years