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Transcription Factor 7-Like 2 (*TCF7L2*) Polymorphism and Hyperglycemia in an Adult Italian Population-Based Cohort

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OBJECTIVE — To assess whether *TCF7L2* polymorphism has a role in the deterioration of glycemic control.

RESEARCH DESIGN AND METHODS — Metabolic variables were evaluated at baseline and after 6-year follow-up in 1,480 Caucasian subjects from a population-based cohort.

RESULTS — At baseline, T-allele carriers showed significantly lower BMI and homeostasis model assessment for β-cell function (HOMA-B) values and higher fasting glycemia and diabetes prevalence. At follow-up, fasting glucose and HOMA-B index were increased and reduced, respectively, in carriers of the T-allele. Incident impaired fasting glucose (IFG) and incident diabetes were 5.7, 10.7, 16.9% and 1.6, 1.7, 3.0% in the CC, CT, and TT genotypes, respectively. In a multiple logistic regression model, the association between incident IFG and the T-allele was significant (odds ratio [OR] 2.08 [95% CI 1.35–3.20] and 3.56 [2.11–5.98] in CT and TT genotypes, respectively).

CONCLUSIONS — The T-allele of *TCF7L2* rs7903146 polymorphism was independently associated with increasing fasting glucose values toward hyperglycemia in the follow-up.

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Among the variety of *TCF7L2* polymorphisms correlating with type 2 diabetes, the single nucleotide polymorphism (SNP) rs7903146 has shown the strongest association with the disease (1). We investigated the association of the SNP rs7903146 with *1*) type 2 diabetes or *2*) impaired fasting glucose (IFG) or *3*) the metabolic syndrome (MS) in an adult Italian population-based cohort both cross-sectionally and after 6-year follow-up.

RESEARCH DESIGN AND METHODS

— All 1,877 Caucasians aged 45–64 years and representative of the province of Asti (Italy) were invited to participate in a metabolic survey in 2001–2003; 1,658 (88.3%) agreed to participate by written informed consent. Both participants and nonparticipants were similar to the resident population of corresponding age with respect to sex composition, level of education, prevalence of known diabetes, and living in a rural area (2). Diabetes and MS were diagnosed according to published recommendations and criteria (3,4); the homeostasis model assessment-insulin resistance (HOMA-IR) index and the HOMA for β-cell (HOMA-B) function were calculated (5).

Genotyping for *TCF7L2* SNP rs7903146 utilized the real-time allele discrimination method (Applied Biosystems, Foster City, CA). All procedures were in accordance with the Declaration of Helsinki and approved by the local ethics committee.

HOMA-IR, HOMA-B, insulin, and triglyceride values were log-transformed and used in all analyses. Multiple regression analyses (for continuous variables) or multiple logistic regression analyses (for dichotomic variables) were used to evaluate the associations between each variable and the presence of the CT or TT genotypes (introduced in the model as dummy variables) after adjustments for age, sex, familial diabetes, BMI, and waist circumference. The capacity of the TT genotype for predicting incident IFG and diabetes was examined by calculating the receiver operating characteristics (ROC) curves and the area under the curve (AUC).

RESULTS

— From January to November 2008, patients were contacted for a follow-up visit: 1,480/1,658 (89.3%) were evaluated after excluding those who died ($n = 61$) and those whose blood samples were not available for genotyping ($n = 117$). Mean follow-up was 6.1 ± 0.34 years. At baseline, 25.1% of patients were on anti-hypertensive treatment and 4.7% were on hypoglycemic drugs.

Characteristics at baseline and follow-up of subjects grouped by genotypes are presented in Table 1. The rs7903146 genotypic distribution was in Hardy-Weinberg equilibrium.

At baseline, carriers of the T-allele showed significantly higher values of fasting glucose and lower BMI and HOMA-B index values in a regression model (Table 1). Prevalence of diabetes was significantly higher in subjects carrying the minor T-allele in a multiple logistic regression model, while no significant differences were detected for prevalence of IFG and MS.

At follow-up, fasting glucose and HOMA-B values were increased and reduced, respectively, in T-allele carriers. In these patients, prevalence of IFG, diabetes, and MS were significantly higher in a multiple logistic regression model in both CT and TT genotypes (OR 1.78 [95% CI 1.06–2.99] and 3.10 [1.63–5.91] for diabetes; 1.81 [1.31–2.51] and [1.90–4.39] for IFG; 1.34 [1.02–1.75] and 1.79 [1.22–2.64] for MS in CT and TT genotypes, respectively). The association between T-allele and MS was exclusively

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Table 1—*Characteristics at baseline and follow-up by* TCF7L2 *rs7903146 genotypes*

	At baseline				
	CC	CT	*P* (95% CI)	TT	*P* (95% CI)
n	580	699		201	
Frequency (%)	39.1	47.2		13.7	
Male (%)	47.8	47.8	0.92* (0.98–1.02)	49.8	0.60* (0.80–1.46)
Diabetes in parents (%)	26.7	25.6	0.65* (0.73–1.21)	31.8	0.16* (0.90–1.82)
Age (years)	54.5 ± 5.7	54.7 ± 5.5	0.53† (−0.42 to 0.82)	54.2 ± 5.7	0.49† (−0.58 to 1.22)
BMI (kg/m^2)	27.0 ± 4.9	26.6 ± 4.6	0.12† (−0.11 to 0.91)	26.0 ± 4.0	0.01† (−1.70 to −0.22)
Waist (cm)	92.3 ± 13.2	91.7 ± 12.7	0.39† (−2.04 to 0.78)	89.9 ± 12.5	0.02† (−4.48 to −0.35)
SBP (mmHg)	133.9 ± 16.4	134.1 ± 15.6	0.57‡ (−1.18 to 2.12)	133.6 ± 15.9	0.52‡ (−1.60 to 3.18)
DBP (mmHg)	83.7 ± 9.4	83.4 ± 9.3	0.83‡ (−1.07 to 0.87)	82.5 ± 9.0	0.83‡ (−2.06 to 0.79)
LDL-C (mM/l)	3.3 ± 1.0	3.3 ± 0.9	0.95‡ (−0.10 to 0.09)	3.4 ± 0.9	0.47‡ (−0.09 to 0.21)
HDL-C (mM/l)	1.6 ± 0.4	1.5 ± 0.3	0.13‡ (−0.06 to 0.008)	1.6 ± 0.4	0.78‡ (−0.04 to 0.06)
Triglycerides (mM/l)	1.3 (0.9)	1.3 (0.8)	0.59‡ (−0.06 to 0.04)	1.2 (0.7)	0.21‡ (−0.11 to 0.03)
Glucose (mM/l)	5.7 ± 1.4	5.9 ± 1.5	0.02‡ (0.04–0.38)	6.2 ± 2.7	<0.001‡ (0.37–0.87)
Insulin (pM/l)	40.8 (21.6)	40.8 (19.8)	0.86‡ (−0.03–0.04)	40.2 (16.2)	0.005 ‡ (−0.12 to −0.02)
HOMA-B (μU/ml/mM/l)	79.4 (44.6)	74.3 (44.6)	−0.13 to −0.03 *P* = 0.004‡	73.2 (40.9)	−0.29 to −0.13 p = <0.001‡
HOMA-IR (mM/l × μU/ml)	1.7 (1.0)	1.7 (1.0)	0.12‡ (−0.01 to 0.08)	1.7 (0.8)	0.90‡ (−0.07 to 0.06)
Diabetes (%)	3.8	6.6	0.01# (1.16–3.59)	8.0	0.006# (1.36–5.64)
Incident diabetes (%)					
IFG (%)	12.9	15.3	0.18# (0.90 to −1.72)	15.9	0.16# (0.88–2.20)
Incident IFG (%)					
MS (%)	24.1	24.3	0.49# (0.83–1.48)	18.9	0.70# (0.58–1.44)

Data are means ± SD or median (interquartile range) for not-normally distributed values. **P* values calculated by a linear logistic regression analysis by evaluating the association of gender or diabetes in parents with CT and TT genotypes; †*P* values calculated by a linear regression analysis by evaluating the association of age or BMI or waist circumference with CT and TT genotypes; ‡*P* values calculated by a multiple regression analysis by evaluating the association of each of the variables marked (one model for each variable) with CT and TT genotypes after adjusting for age, sex, BMI, waist circumference, and familial diabetes; #*P* values calculated by a multiple logistic regression analysis by evaluating the association of each of the variables marked (one model for each variable) with CT and TT genotypes after adjusting for age, sex, BMI, waist circumference, and familial diabetes; §data available in 1,031 subjects. DBP, diastolic blood pressure; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic blood pressure.

due to the higher prevalence of hyperglycemia in these subjects.

Incident diabetes was almost double in homozygous for the T-allele, but the association was not significant due to the low case number. Incident IFG was twofold and threefold higher in the heterozygous and homozygous T carriers, respectively (OR 2.08 [95% CI 1.35–3.20] and 3.56 [2.11–5.98] in CT and TT genotypes, respectively). Adjustments for smoking habits, lipid parameters, or HOMA-B values did not significantly affect the results. The AUCs of the ROC curves for the TT genotype were 0.56 for incident IFG and 0.54 for incident diabetes.

CONCLUSIONS — The major findings of the present study are: *1*) a high prevalence of the defective T-allele in an Italian population-based cohort; *2*) a significant association between the T-allele and hyperglycemia and β-cell dysfunction at baseline and follow-up; *3*) a two- to threefold higher risk of incident IFG in the T-allele carriers at follow-up; and *4*) an increased prevalence of MS in the T-allele carriers.

The minor T-allele is strongly associated with reduced HOMA-B levels, suggesting that the polymorphism could affect the ability of the β-cells to secrete insulin. These data indicate that SNP rs7903146 polymorphism may modulate the degree of insulin secretion to offset the prevailing level of insulin resistance without being a cause of insulin resistance. SNP rs7903146 acts like other *TCF7L2* polymorphisms, such as rs12255372 (6). The T-allele is significantly associated with lower BMI, so we can confirm recent studies that suggest that the variants do not have a primary effect on adiposity (7). These studies showed that individuals with the highest risk genotype and the lowest birth weight had the greatest risk of type 2 diabetes (8).

It has been reported that *TCF7L2* exerts its influence through an impairment of insulin secretion. This impairment was reportedly due to a functional defect in the glucagon-like peptide-1 (GLP-1) signaling in β-cells and not due to defective/failing GLP-1 secretion (9). It is unlikely that the pathway of incretins by itself can play a central role in the pathophysiology of type 2 diabetes. We reported that *TCF7L2* may impact β-cell function both directly through modulating β-cell response to glucose and indirectly by modulating incretin action or secretion (10).

The prevalence of MS in subjects carrying the TT genotype was about twofold higher at follow-up when compared with the prevalence at baseline. This increment was almost exclusively due to the significantly higher prevalence of hyperglycemia in this subgroup. The AUC values are similar to those reported in literature dealing with one single SNP (11).

Our study confirms an effect of the widely replicated *TCF7L2* rs7903146 polymorphism on hyperglycemia in an adult Italian population-based cohort both in cross-sectional and longitudinal evaluation. The independent association of *TCF7L2* polymorphism with increasing fasting glucose values in the follow-up may represent a marker for higher metabolic risk, which is useful for developing

Table 1—*Continued*

		At follow-up		
CC	CT	*P* (95% CI)	TT	*P* (95% CI)
580	699		201	
39.1	47.2		13.7	
60.6 ± 5.7	60.8 ± 5.6	0.51† (−0.41 to 0.83)	60.3 ± 5.8	0.50† (−0.59 to 1.22)
27.1 ± 4.9	26.9 ± 4.6	0.41 (−0.72 to 0.29)	26.2 ± 3.9	0.02† (−1.65 to −0.17)
93.6 ± 13.1	93.4 ± 13.0	0.74† (−1.63 to 1.15)	92.1 ± 10.4	0.14† (−3.56 to 0.52)
134.8 ± 16.8	136.4 ± 17.8	0.003‡ (0.18–3.66)	134.6 ± 16.4	0.34‡ (−1.30 to 3.78)
82.9 ± 9.9	83.4 ± 9.4	0.14‡ (−0.25 to 1.73)	82.3 ± 8.5	0.88‡ (−1.56 to 1.34)
3.5 ± 1.0	3.6 ± 1.0	0.50‡ (−0.07 to 0.15)	3.6 ± 1.1	0.71‡ (−0.13 to 0.19)
1.5 ± 0.4	1.4 ± 0.4	0.39‡ (−0.06 to 0.02)	1.5 ± 0.4	0.51‡ (−0.08 to 0.04)
1.3 (0.9)	1.3 (0.8)	0.43‡ (−0.03 to 0.07)	1.2 (0.8)	0.75‡ (−0.08 to 0.06)
5.3 ± 0.9	5.7 ± 1.2	<0.001‡ (0.30–0.54)	6.1 ± 1.7	<0.001‡ (0.60–0.96)
45.5 (38.8)§	44.9 (34.3)§	0.54‡ (−0.11 to 0.06)	43.6 (31.1)§	0.005‡ (−0.30 to −0.06)
97.2 (85.4)§	85.5 (74.6)§	−0.25 to −0.05 *P* = 0.005‡	75.4 (70.4)§	−0.50 to −0.20 *P* = <0.001‡
1.7 (1.6)§	1.8 (1.5)§	0.12‡ (−0.02 to 0.16)	1.9 (1.3)§	0.20‡ (−0.04 to 0.22)
4.5	7.0	0.03# (1.06–2.99)	10.5	<0.001# (1.63–5.91)
1.6	1.7	0.75# (0.48–2.78)	3.0	0.15# (0.75–6.37)
11.2	18.0	<0.001# (1.31–2.51)	25.4	<0.001# (1.90–4.39)
5.7	10.7	<0.001# (1.35–3.20)	16.9	<0.001# (2.11–5.98)
27.9	31.5	0.04# (1.02–1.75)	33.3	0.003# (1.22–2.64)

more closely tailored lifestyle preventive approaches as we have recently reported (12).

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

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