Association of the rs7903146 single nucleotide polymorphism at the Transcription Factor 7-like 2 (*TCF7L2*) locus with type 2 diabetes in Brazilian subjects

Associação do polimorfismo de nucleotídeo único rs7903146 no locus do TCF7L2 com diabetes tipo 2 em indivíduos brasileiros

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ABSTRACT

Objective: To investigate the association of the T allele of the single nucleotide polymorphism (SNP) rs7903146 of *TCF7L2* with the occurrence of T2D in a sample of subjects followed up at the Brasilia University Hospital. **Subjects and methods:** The SNP rs7903146 of *TCF7L2* was genotyped by allele-specific PCR in 113 patients with known T2D and in 139 non-diabetic controls in Brasilia, Brazil. **Results:** We found that the T allele of the SNP rs7903146 of *TCF7L2* was significantly associated with T2D risk (odds ratio of 3.92 for genotype TT in the recessive genetic model, p = 0.004 and 1.5 for T allele, p = 0.032). **Conclusion:** These results reinforce previous findings on the consistent association of this genetic factor and the risk of T2D in populations of diverse ethnic backgrounds. Arq Bras Endocrinol Metab. 2012;56(8):479-84

Keywords
TCF7L2; single nucleotide polymorphism; type 2 diabetes; rs7903146

RESUMO

Objetivo: Investigar a associação do alelo T do polimorfismo de nucleotídeo único (SNP) rs7903146 do *TCF7L2* com a ocorrência de DM2 em uma amostra de indivíduos acompanhados no Hospital Universitário de Brasília. **Sujeitos e métodos:** O SNP 7903146 do *TCF7L2* foi genotipado por PCR alelo-específica em 113 pacientes portadores de DM2 e em 139 controles não diabéticos em Brasília, Brasil. **Resultados:** Foi observada associação significativa do alelo T do SNP rs7903146 do *TCF7L2* com a ocorrência de DM2 (razão de chances de 3,92 para o genótipo TT utilizando o modelo genético recessivo, p = 0,003; e de 1,5 para o alelo T, p = 0,032). **Conclusão:** Esse resultado reforça os achados prévios de associação consistente desse fator genético com o risco de diabetes em populações de origens étnicas diversas. Arq Bras Endocrinol Metab. 2012;56(8):479-84

Descritores
TCF7L2; polimorfismo de nucleotídeo único; diabetes tipo 2; rs7903146

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INTRODUCTION

Type 2 diabetes (T2D) is a heterogeneous group of metabolic disorders characterized by the inability of pancreatic beta cells to increase insulin secretion in order to compensate for insulin resistance (1). It represents a significant worldwide burden due to the alarming increase in its incidence over the last decades (2,3), and because of its significant morbidity and mortality rates (4).

Environment and lifestyle changes are believed to play a primary role in the current epidemic of T2D, but the inherent susceptibility to the disease is widely

attributed to complex genetic factors. There is compelling evidence that genetic susceptibility to the disease is polygenic, and genome-wide association studies have thus far identified almost 50 loci associated with T2D risk (5-8). Many of the genetic variants identified to date have been associated with small effect sizes, although single nucleotide polymorphisms (SNP) at the transcription factor 7-like 2 gene (*TCF7L2*) locus on chromosome 10q have been strongly and consistently associated with T2D risk in various populations and ethnic groups (6,9-11). An intronic SNP at this locus in particular, rs7903146, is considered the most important known genetic risk factor for T2D development (10).

TCF7L2 encodes the transcription factor TCF7L2, involved in the Wnt signaling pathway, which seems to be critical to pancreatic islet development and adipogenesis (12). TCF7L2 forms heterodimers with beta-catenin to induce the expression of various genes, including the gene encoding the insulinotropic hormone glucagon-like peptide 1 (13), the insulin gene (14), and genes that encode proteins involved in processing and exocytosis of insulin granules (15). Although the mechanisms underlying the association of *TCF7L2* polymorphisms and alterations in glucose homeostasis are not clear, these data suggest that this transcription factor primarily affects insulin secretion. *TCF7L2* polymorphisms seem to influence beta cell function (6,16-19) and insulin sensitivity (20-22).

Although disease association studies have shown that the T allele of the rs7903146 SNP at the *TCF7L2* locus is strongly associated with T2D risk in diverse ethnic groups, it is noteworthy that the frequency of SNPs at this locus was shown to be different in the various populations included in these studies. The T allele of rs7903146 SNP at the *TCF7L2* was seen in 18-42% of non-diabetic European and Arab populations (23-25), but in less than 5% of healthy individuals in studies with Southeast Asian populations (26,27). These data might suggest that the effect size of this SNP on T2D risk may vary among populations worldwide.

Marquezine and cols. reported that the T allele of rs7903146 SNP at the *TCF7L2* locus is associated with a 1.57 increase in the risk of T2D in a sample of patients with documented multivessel coronary artery disease from the multivessel coronary disease patient studies (MASS II Study) in Southeastern Brazil, although this genetic variant did not increase the accuracy of a validated diabetes risk prediction score for the

Brazilian population (28). We have previously shown a 37% frequency of the T allele of rs7903146 SNP at the *TCF7L2* locus in a group of 104 healthy young volunteers (mean age of 27.7 ± 11 years) randomly selected in Brasilia, the capital of Brazil (29). The Brazilian population represents a heterogeneous ethnic group, and Brasilia is a relatively young city; its population comprises individuals from almost all regions of the country. In this study, we describe the frequency of the alleles of the rs7903146 SNP at the *TCF7L2* locus, and the association between the T allele of this polymorphism and the occurrence of T2D in a small sample of the population followed up at the Brasilia University Hospital.

SUBJECTS AND METHODS

Subjects

A total of 252 subjects were enrolled in this study, all from population seen at the Brasilia University Hospital, Brasilia, Brazil. The patients (113) were not related, aged over 40 years, and had been diagnosed with T2D after the age of 30 years, in accordance with 2006 American Diabetes Association (ADA) (30); individuals with features suggestive of other types of diabetes were excluded from the study. Control subjects (139) with normal glucose tolerance were also not related, aged over 40 years, and were seen for disorders not related to *diabetes mellitus* at the Brasilia University Hospital. Written informed consent was obtained from each participant after a full explanation of the study, which was approved by the Ethics Committee of the Health Sciences School from the University of Brasilia.

Clinical and biochemical data

The following clinical and biochemical data were obtained from the medical records of diabetic patients: family history of T2D, personal history of hypertension, dyslipidemia, hyperuricemia, nonalcoholic fatty liver disease, microvascular chronic complications (nephropathy, retinopathy, and neuropathy), smoking status (previous and current), presence of *acantosis nigricans*, body mass index (weight in kg/height in m²), waist circumference, fasting and postprandial blood glucose, serum lipid profile, serum urea, creatinine, uric acid, and liver enzymes. Complete information was not available for all patients.

rs7903146 genotyping

A venous blood sample (5 mL) was obtained by peripheral venipuncture using disposable material and EDTA-containing tubes from each patient. All samples were collected at the Brasilia University Hospital. DNA was extracted by the Chelex-100 method (31), and rs7903146 genotype assays were conducted by allele-specific polymerase chain reaction. The primers and conditions for this reaction have been described elsewhere (29).

Statistical analyses

Categorical data were described in terms of absolute and relative frequencies, and were analyzed using Fisher's exact test. Numerical data were expressed as means ± standard deviations. Hardy-Weinberg equilibrium and the association between disease status and the genetic variant were tested by Pearson's χ^2 test, which was also used to find the best genetic model of inheritance that described effect of the rs7903146 SNP at the *TCF7L2* locus. Odds Ratios, 95% confidence intervals (95%CI), and all statistical tests were carried out using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, California, USA (www.graphpad.com). A *p* value < 0.05 was considered statistically significant.

RESULTS

Mean age of patients was 58.6 ± 9.8 years, and 76.9% were female. In the control group, mean age was 56.5 ± 9.9 years, and the majority was also female (84.1%). Mean age (p = 0.063) and gender distribution were similar (χ^2 = 2.08, df = 1, p = 0.14) in both groups. Demographic, clinical, and biochemical parameters from T2D patients are described in table 1.

Allele and genotype frequencies of the rs7903146 SNP at *TCF7L2* are summarized in table 2. Deviation from the Hardy-Weinberg equilibrium was not seen in either T2D (χ^2 = 3.14, df = 1, p = 0.08), or the control group (χ^2 = 1.03, df = 1, p = 0.31). Association analyses, which were performed using the chi-square test with 2 degrees of freedom, yielded a significant association between rs7903146 SNP of *TCF7L2* and disease susceptibility (χ^2 = 8,7, df = 2, p = 0.012). To investigate in which model the effect of rs7903146 SNP at the *TCF7L2* would fit, dominant, recessive, and co-dominant genetic models were considered (Table 2). Analy-

sis performed in the recessive genetic model, with two copies of T being required for increased risk, yielded the strongest association between rs7903146 and T2D (χ^2 = 8.64, df = 1, p = 0.003; Table 2). No significant associations were observed in the dominant (χ^2 = 1.22, df = 1, p = 0.26) and co-dominant (χ^2 = 0.35, df = 1, p = 0.55) model of inheritance. Chi-square statistics also indicated a significant association between the TT genotype and T2D compared with the CC reference genotype (χ^2 = 8.3; df = 1; p = 0.004), and yielded an odds ratio of 4.04 (95% CI; 1.48-11.0). The same analysis was carried out for heterozygotes, and it showed that the CT genotype was not significantly associated with T2D (χ^2 = 0.06, df = 1, p = 0.81), yielding an odds ratio of 1.07 (95% CI; 0.63-1.80). Moreover, allelic odds ratio of rs7903146 T carriers was 1.51 (95% CI; 1.03-2.21; P = 0.032; Table 2).

Table 1. Clinical and biochemical characteristics of T2D patients

Characteristics of T2D patients	Mean ± SD	n
Age (years)	58.6 ± 9.8	113
Gender (female)	76.9	113
Current smoking (%)	7.9	89
Previous smoking (%)	40.0	80
Family history of diabetes (%)	79.3	87
Acanthosis nigricans (%)	42.5	73
Hypertension (%)	78.8	85
Dyslipidemia (%)	77.2	79
Hyperuricemia (%)	30.2	63
Hepatic steatosis (%)	3.7	54
Diabetic nephropathy (%)	35.3	68
Diabetic retinopathy (%)	21.2	66
Diabetic neuropathy (%)	26.6	79
Body mass index (kg/m²)	29.1 ± 4.9	78
Waist circumference (cm)	100.7 ± 11.3	47
Fasting glucose (mg/dL)	147.6 ± 59.5	66
Postprandial glucose (mg/dL)	209.2 ± 108.7	36
Total cholesterol (mg/dL)	203.4 ± 56.9	62
HDL cholesterol (mg/dL)	42.3 ± 13.9	62
LDL cholesterol (mg/dL)	118.2 ± 43,1	62
Triglycerides (mg/dL)	217 ± 156.6	62
Urea (mg/dL)	36.8 ± 13.2	61
Creatinine (mg/dL)	0.85 ± 0.26	61
Uric acid (mg/dL)	5.4 ± 1.3	43
Alanine aminotransferase (U/L)	22.6 ± 8.7	56
Aspartate aminotransferase (U/L)	23.39 ± 10.2	56

n: total number of patients with data retrieved from hospital records; SD: standard deviation.

Table 2. Genotypes, alleles, and statistical data of rs7903146 SNP at the TCF7L2 in diabetic and control subjects

Genotype distribution				
	CC	**CT**	**TT**	**Total**
T2D	49 (43.4%)	47 (41.6%)	17 (15%)	113
Controls	70 (50.4%)	63 (45.6%)	6 (4.3%)	139
Total	119	110	23	252
Allelic distribution				
	C		**T**	**Total**
T2D	145 (64.2%)		81 (35.8%)	226
Controls	203 (73%)		75 (27%)	278
Total	348		156	504
Genetic models and statistical data				
Genetic Model	**Odds ratio (95% CI)**	**Chi-square**	**Degrees of freedom**	**P**
Association (CC *vs.* CT *vs.* TT)		8.70	2	0.012
Dominant (CT + TT *vs.* CC)	1.32 (0.80-2.18)	1.22	1	0.260
Recessive (TT *vs.* CT + CC)	3.92 (1.49-10.3)	8.64	1	0.003
Co-dominant (CT *vs.* CC + TT)	1.16 (0.70-1.92)	0.35	1	0.55
Homozigote (CC *vs.* TT)	4.04 (1.48-11.0)	8.30	1	0.004
Heterozigote (CC *vs.* CT)	1.06 (0.63-1.80)	0.06	1	0.81
Allele (C *vs.* T)	1.51 (1.03-2.21)	4.58	1	0.032

DISCUSSION

The identification of genetic variants influencing T2D is a major focus of research to improve the understanding of the mechanisms underlying the pathogenesis of this disorder. Recent advances, such as the development of genome-wide association studies have enabled the identification of a number of genes associated with T2D risk. In this scenario, common genetic variants in *TCF7L2* gene were recently associated with T2D risk by Grant and cols. (9), and these findings were consistently reproduced in various populations (6,10,11). Since then, *TCF7L2* has been considered one of the most important known genetic risk factors for the development of the disease.

In this study, the association of the rs7903146 polymorphism at the *TCF7L2* and diabetes risk was found in a small sample from the population of Brasilia, in the Central Western region of Brazil. The odds ratio for the association with genotype TT (recessive model) were 3.92 (CI 95%; 1.49-10.3); and for T allele 1.51 (CI 95%; 1.03-2.21), similar to that reported in the previous study involving the Brazilian population (28), as well as in other populations (10,25,32). The T allele was significantly more frequent in T2D patients than in controls (35.8% *versus* 27%; p = 0.032). The frequency of the risk allele in the control group was similar to

that described in non-diabetic European (Cauchi, 2006 and Gonzalez, 2008) and Arab (Ezzidi, 2009) populations, and higher than that reported in Southeast Asian populations, in which this variant occurs in less than 5% of the general population (Chang, 2007; Wen, 2010).

The frequency of the T allele of rs7903146 SNP at the *TCF7L2* in both T2D and control subjects was lower than our previously reported frequency (37%). The difference in the mean age of subjects enrolled in each study (27.7 ± 11 *versus* 58.6 ± 9.8 and 56.5 ± 9.9 years in T2D and controls, respectively), and it is be possible that the subjects enrolled in the first study may be representative of a group at higher risk of developing T2D with advancing age, since the frequency of the T allele in this group was more similar than that found in T2D patients in this study.

Despite the strong association between rs7903146 polymorphism at the *TCF7L2* and T2D risk in clinical studies, it is not readily apparent how this intronic *TCF7L2* variant increases susceptibility to the disease. There is evidence that *TCF7L2* has an important role in maintaining beta cell mass and function. This transcription factor itself seems to be critical for beta cell proliferation, protection against apoptosis, and insulin secretion (14,33). In addition, it has been shown to be involved in the expression of glucagon-like peptide 1,

and gastric inhibitory peptide receptors in beta cells, which mediate the effects of the correspondent incretin hormones to promote beta cell proliferation, neogenesis, and survival in rodent models (34). More recently, TCF7L2 expression in the endocrine pancreas was correlated not only with beta cell proliferation, but also with beta cell regeneration in different murine models of diabetes (35). In the same study, it was shown that in human exocrine pancreatic tissue, *TCF7L2* overexpression induced beta cell phenotype and insulin production in ductal epithelial cells (35).

Our results confirm the previous findings from Marquezine and cols. (28), who studied a population from a different region of Brazil. Replication of the association of this genetic variant with T2D risk in a small Brazilian sample reinforces the strength of this association in our population and worldwide. However, it is important to point out that in spite of all the efforts to understand how the T allele of SNP rs7903146 at the *TCF7L2* is precisely related to T2D risk, clinical studies have failed to show that determination of *TCF7L2* genotype adds to clinical criteria in determining the individual risk of the disease. Hence, although it is believed that knowledge of genetic factors associated with T2D risk has the potential to bring new perspectives to the development of more effective preventative and therapeutic strategies for the disease, there is a lot to be understood before this information can be translated into benefits in clinical practice.

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