Association between -1082G/A, -819C/T, and -592C/A genetic polymorphisms in *IL-10* and risk of type 2 diabetes mellitus in a Chinese population

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ABSTRACT. Type 2 diabetes mellitus is the most common form of endocrine disease in humans; genetic factors are known to contribute to the development of this disease. In this case-control study, we investigated the relationship between the -1082G/A, -819C/T, and -592C/A polymorphisms in interleukin 10 (*IL-10*) and the pathogenesis of type 2 diabetes mellitus in a Chinese population. Patients with type 2 diabetes mellitus (N = 228) and control subjects (N = 240) were recruited from the Department of Endocrinology at the People's Hospital of Linyi City, between September 2013 and April 2015. The *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms were genotyped by polymerase chain reaction-restriction fragment length polymorphism. Multivariate logistic regression analyses revealed that patients carrying the AA genotype of *IL-10* -592C/A were at a higher risk of developing type 2

diabetes mellitus compared to those carrying the CC genotype [adjusted odds ratio (OR) = 1.74; 95% confidence interval (CI) = 1.03-2.95]. In addition, individuals carrying the A allele of *IL-10* -592C/A showed a 1.34-fold higher risk of developing type 2 diabetes mellitus compared to those carrying the C allele (adjusted OR = 1.34; 95%CI = 1.03-1.75). There was no significant correlation between the *IL-10* -1082G/A and -819C/T polymorphisms and risk of type 2 diabetes mellitus. In conclusion, this study shows that the -1082G/A polymorphism of *IL-10* contributes to the onset of type 2 diabetes mellitus, and may be considered a biomarker for early screening of type 2 diabetes mellitus in the Chinese population studied here.

Key words: *IL-10*; Polymorphism; Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus, a chronic and complex disease, is a challenging problem that severely threatens public health. The development of type 2 diabetes mellitus occurs over a long period; and many environmental and lifestyle factors such as obesity, high dietary fat and glucose content, tobacco smoking and alcohol drinking habits play a vital role in its development (He et al., 2015; Nguyen et al., 2015; Osonoi et al., 2016). Hereditary or genetic factors have also been reported to play an important role in the development of this disease. For example, polymorphisms in genes coding for transcription factor 7-like 2 (*TCF7L2*), vitamin D receptor, glutathione S-transferases, ATP-binding cassette transporter A1, and N-acetyltransferase 1 and 2 are correlated with risk of diabetes (Al-Shaqha et al., 2015; Haghvirdizadeh et al., 2015; Jia et al., 2015; Liu et al., 2015; Stoian et al., 2015).

Interleukin-10 (IL-10) is an immunoregulatory cytokine secreted by monocyte-macrophages and lymphocytes. Previous studies have reported that *IL-10* prevents the development of many diseases in animal disease models, such as collagen arthritis, sepsis, and pancreatitis (Gérard et al., 1993; Walmsley et al., 1996; Kolb, 1997). This indicates that IL-10 plays a protective, anti-inflammatory role in the host. Three single nucleotide polymorphisms in the promoter region of *IL-10* [-1082G/A (rs1800896), -819C/T (rs1800871), and -592C/A (rs1800872)] have been previously shown to alter the structure and expression of IL-10 by affecting the gene function (Glocker et al., 2011). Previous studies also reported that polymorphisms in *IL-10* are associated with the development of type 2 diabetes mellitus, but with conflicting results (Saxena et al., 2012, 2013; Zhang et al., 2013; Bai et al., 2014). In this case-control study, we investigated the relationship between the *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms and pathogenesis of type 2 diabetes mellitus in a Chinese population.

MATERIAL AND METHODS

Subjects

Patients with type 2 diabetes mellitus (N = 228) and control subjects (N = 240) were recruited from the Department of Endocrinology at the People's Hospital of Linyi City, between September 2013 and April 2015. Type 2 diabetes mellitus was diagnosed based on

the criteria specified by the World Health Organization-International Diabetes Federation.

The control subjects were selected from among individuals who received regular physical examinations at the People's Hospital of Linyi City. All control subjects were confirmed to be free of type 2 diabetes mellitus. Subjects with a history of type 2/type 1 diabetes mellitus, endocrine diseases, end-stage liver or kidney disease, acute or chronic diseases, acute complications, cardiovascular diseases, malignant tumors, and/or autoimmune diseases were excluded from this study.

The basic demographic and lifestyle information of all patients and control subjects was obtained from a face-to-face interview, based on a self-designed questionnaire. The clinical information of all recruited subjects was collected from their medical records.

At the time of enrollment, the mean ages of the patients and controls were 55.63 ± 8.64 years and 54.51 ± 8.52 years, respectively. Seventy-eight patients with type 2 diabetes mellitus (34.21%) were female and 150 (65.79%) were male, while the control group was composed of 104 (43.33%) females and 136 (56.67%) males. Peripheral venous blood (5 mL) was obtained from all patients and control subjects, and stored in tubes coated with ethylenediaminetetraacetic acid (EDTA) in a refrigerator. Signed informed consent forms were obtained from all patients and control subjects prior to enrollment. The study design was approved by the Clinical Research Ethics Committee of our hospital.

Genotyping analysis

DNA was extracted from the peripheral venous blood samples, using the Tiangen DNA Blood Mini Kit (Tiangen Biotech Co., Ltd., Beijing, China). The *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms were genotyped by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). The primer sequences were designed using Primer Premier 5.0. The primer sequences for *IL-10* -1082G/A, -819C/T, and -592C/A are provided in Table 1. The PCR conditions were set as follows: an initial denaturation 95°C for 5 min; 35 cycles of denaturation at 94°C for 40 s, annealing at 62°C for 25 s, and extension at 72°C for 25 s; and a final extension at 72°C for 6 min. The PCR products of the *IL-10* -1082G/A, -819C/T, and -592C/A polymorphic sites were digested using the restriction enzymes *Mnl*I, *Mae*III, and *Rsa*I, respectively. The PCR products were then electrophoresed on a 1.5% agarose gel, and analyzed in a fully automated gel image analyzer.

Table 1. Primer sequences for the interleukin 10 (*IL-10*) -1082G/A, -819C/T, and -592C/A polymorphisms.

IL-10 polymorphism	Forward primer (5'→3')	Reverse primer (3'→5')
-1082G/A	CCTATCCCTACTTCCCCTTCC	GCAACCCAACTGGCTCCC
-819C/T	GGCACTGGTGTACCCTTGTA	CATGACCCCTACCGTCTCTATTTT
-592C/A	GGTAAAGGAGCCTGGAACACATC	GCCCTTCCATTTTACTTTCCAGAGA

Statistical analysis

Significant differences among the groups were determined by performing either the Fisher exact test or Student *t*-test. Multivariate logistic regression analyses were performed to estimate the relationship between the *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms and development of type 2 diabetes mellitus. The results were estimated using the adjusted odds ratios (ORs), 95% confidence intervals (95%CI), and their corresponding P values. Deviation

of the genotype frequencies of the *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms from the Hardy-Weinberg equilibrium were calculated by performing the chi-square test. All statistical analyses were performed using the SPSS 20.0 package (SPSS Inc., Chicago, IL, USA). A P value <0.05 indicated a statistically significant difference.

RESULTS

The patients with type 2 diabetes mellitus and control subjects were comparable in terms of age (t = 1.41, P = 0.08), tobacco smoking status (χ^2 = 1.88, P = 0.17), and alcohol consumption status (χ^2 = 3.46, P = 0.06) (Table 2). However, we identified significant differences in the gender (χ^2 = 4.09, P = 0.04), body mass index (χ^2 = 7.56, P < 0.001), hypertension status (χ^2 = 11.34, P = 0.001), fasting plasma glucose level (t = 14.77, P < 0.001), and fasting insulin level (t = 11.61, P < 0.001) between the patients and control subjects.

Table 2. Baseline information for the patients with type 2 diabetes mellitus and control subjects enrolled in this study.

Variables	Patients (N = 228)	%	Controls (N = 240)	%	χ^2-test or t-test	P value
Age, years	55.63 ± 8.64		54.51 ± 8.52		1.41	0.08
Gender						
Female	78	34.21	104	43.33		
Male	150	65.79	136	56.67	4.09	0.04
Body mass index, kg/m^2	27.10 ± 5.32		24.23 ± 2.45		7.56	<0.001
Tobacco smoking						
No	147	64.47	169	70.42		
Yes	81	35.53	71	29.58	1.88	0.17
Alcohol consumption						
No	137	60.09	164	68.33		
Yes	91	39.91	76	31.67	3.46	0.06
Hypertension						
No	140	61.40	182	75.83		
Yes	88	38.60	58	24.17	11.34	0.001
Fasting plasma glucose, mmol/dL	9.05 ± 3.35		5.01 ± 2.53		14.77	<0.001
Fasting insulin, mmol/dL	62.43 ± 15.75		46.30 ± 14.32		11.61	<0.001

We further analyzed the genotype frequencies of the *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms between the patients and controls (Table 3). Statistical analysis by the chi-square test did not reveal any significant differences in the *IL-10* -1082G/A (χ^2 = 1.49, P = 0.47), -819C/T (χ^2 = 0.36, P = 0.84), and -592C/A (χ^2 = 5.07, P = 0.08) genotype distributions between the patients and controls. The chi-square test also revealed that the genotype distributions of the *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms were in accordance with the Hardy-Weinberg equilibrium in both patients and controls (P > 0.05).

Multivariate logistic regression analyses revealed that patients expressing the AA genotype of *IL-10* -592C/A were at a higher risk of developing type 2 diabetes mellitus compared to those expressing the CC genotype (adjusted OR = 1.74; 95%CI = 1.03-2.95) (Table 4). In addition, individuals carrying the A allele of *IL-10* -592C/A were at a 1.34-fold greater risk of developing type 2 diabetes mellitus compared to those carrying the C allele (adjusted OR = 1.34; 95%CI = 1.03-1.75). However, we did not observe a significant correlation between the *IL-10* -1082G/A and -819C/T polymorphisms and risk of type 2 diabetes mellitus.

Table 3. Genotype distributions of the interleukin 10 (*IL-10*) -1082G/A, -819C/T, and -592C/A polymorphisms in the patients with type 2 diabetes mellitus and control subjects.

IL-10	Patients (N = 228)	%	Controls (N = 240)	%	χ^2-test	P value	Hardy-Weinberg equilibrium	
-1082G/A							Patients	Controls
GG	105	46.05	123	51.25				
GA	99	43.42	97	40.42				
AA	24	10.53	20	8.33	1.49	0.47	0.93	0.89
-819C/T								
CC	77	33.77	87	36.25				
CT	109	47.81	112	46.67				
TT	42	18.42	41	17.08	0.36	0.84	0.75	0.63
-592C/A								
CC	65	28.51	83	34.58				
CA	99	43.42	110	45.83				
AA	64	28.07	47	19.58	5.07	0.08	0.05	0.34

Table 4. Relationship between the interleukin 10 (*IL-10*) -1082G/A, -819C/T, and -592C/A polymorphisms and risk of type 2 diabetes mellitus.

IL–10	Patients	%	Controls	%	Adjusted OR(95%CI)	P value
-1082G/A						
GG	105	46.05	123	51.25	Reference	
GA	99	43.42	97	40.42	1.20 (0.80-1.78)	0.36
AA	24	10.53	20	8.33	1.41 (0.70-2.85)	0.30
Allele						
G	309	67.76	343	71.46	Reference	
A	147	32.24	137	28.54	1.19 (0.89-1.59)	0.22
-819C/T						
CC	77	33.77	87	36.25	Reference	
CT	109	47.81	112	46.67	1.10 (0.72-1.68)	0.65
TT	42	18.42	41	17.08	1.16 (0.66-2.03)	0.59
Allele						
C	263	57.68	286	59.58	Reference	
T	193	42.32	194	40.42	1.08 (0.83-1.42)	0.55
-592C/A						
CC	65	28.51	83	34.58	Reference	
CA	99	43.42	110	45.84	1.15 (0.74-1.80)	0.52
AA	64	28.07	47	19.58	1.74 (1.03-2.95)	0.03
Allele						
C	229	50.22	276	57.50	Reference	
A	227	49.78	204	42.50	1.34 (1.03-1.75)	0.03

[1]Adjusted for age, gender, body mass index, hypertension, fasting plasma glucose, and fasting insulin. OR, Odds ratio; CI, confidence interval.

DISCUSSION

Current genome-wide association studies have identified several genetic loci that play an important role in the development of type 2 diabetes mellitus (Sharma et al., 2015). In this study, we investigated the role of *IL-10* -1082G/A, -819C/T, and -592C/A polymorphisms in the risk of type 2 diabetes mellitus, and identified a relationship between the AA genotype and A allele of *IL-10* -592C/A and pathogenesis of type 2 diabetes mellitus in a Chinese population.

Previous experimental studies indicated that IL-10 contributes to the pathogenesis of type 2 diabetes mellitus (Moritani et al., 1996; Zheng et al., 1997). Moritani et al. (1996) cloned and transferred (adoptive transfer) pancreatic islet-specific CD4+ helper T (Th) 1 cells

to non-obese diabetic mice, and reported that tissue-specific delivery of IL-10 to pancreatic islets with IL-10-transduced Th1 cells contributed to the prevention of autoimmune diabetes (Moritani et al., 1996). Another study reported that IL-10/Fc-treated hosts produce leukocytes that block diabetes expression, thereby delaying the progress of diabetes (Zheng et al., 1997).

IL-10 polymorphisms may induce genetic and molecular aberrations, which could result in the development of several types of autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis, and Crohn's disease, in addition to acute pancreatitis (Amre et al., 2009; Marrakchi et al., 2009; Paradowska-Gorycka et al., 2010; da Silva et al., 2014; Lagha et al., 2015; Li et al., 2015; Talaat et al., 2015). Talaat et al. (2015) reported an association between the clinical features and risk of systemic lupus erythematosus and *IL-10* -1082G/A polymorphisms in an Egyptian population. da Silva et al. (2014) discovered that the *IL-10* -1082G/A polymorphism contributed to susceptibility to systemic lupus erythematosus in a Brazilian population. Lagha et al. (2015) reported an association between the *IL-10* -1082G/A polymorphisms and susceptibility to rheumatoid arthritis. Paradowska-Gorycka et al. (2010) conducted a study involving 244 patients with rheumatoid arthritis and 106 healthy controls, and reported that the *IL-10* -592C/A and -1082G/A polymorphisms may play an important role in the susceptibility to rheumatoid arthritis. Further, Marrakchi et al. (2009) reported that polymorphisms in the *IL-10* promoter region increased the risk of inflammatory bowel disease. Amre et al. (2009) conducted a study on 270 patients with Crohn's disease and 336 control subjects, and reported that *IL-10* -819C/T variants contributed to the onset of Crohn's disease.

Several studies have reported the possible correlation between polymorphisms in *IL-10* and the onset of type 2 diabetes mellitus, but with conflicting results (Ezzidi et al., 2009; Saxena et al., 2012, 2013; Yin et al., 2013; Bai et al., 2014; Chang et al., 2005). Chang et al. (2005) reported that *IL-10* polymorphisms could determine diabetic susceptibility in a Taiwanese population. Ezzidi et al. (2009) performed a study on 515 patients with type 2 diabetes and 402 control subjects, and discovered a correlation between the *IL-10* -819C/T polymorphism and the risk of nephropathy in a Tunisian population. Furthermore, Saxena et al. (2012, 2013) reported that Indian patients harboring the *IL-10* -592C/A polymorphism displayed a greater risk of developing type 2 diabetes mellitus compared to that by the controls. Bai et al. (2014) reported that the *IL-10* -592C/A and -1082G/A polymorphisms increased the risk of type 2 diabetes mellitus in a Chinese population. A recent meta-analysis comprising 10 studies indicated that only the *IL-10* -1082G/A polymorphism contributed to the onset of type 2 diabetes mellitus, while the *IL-10* -819C/T and -592C/A polymorphisms did not (Hua et al., 2013). Discrepancies in these studies could be attributed to differences in population subtypes, selection of patients and controls, and sample sizes.

This study has two limitations. First, the small sample size included in this study could be responsible for the low statistical power of the differences identified between groups. Secondly, selection bias could not be avoided, as the patients and controls were selected from a single hospital in China. Further studies with more samples are warranted to confirm these results.

In conclusion, this study indicates that the *IL-10* -1082G/A polymorphism contributes to the onset of type 2 diabetes mellitus. However, we found no association between the *IL-10* -819C/T and -592C/A polymorphisms and disease development. The *IL-10* -1082G/A polymorphism could be considered a biomarker for early screening of type 2 diabetes mellitus in the Chinese population.

Conflicts of interest

The authors declare no conflict of interest.

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