



Association between the *TRAIL* single nucleotide polymorphism rs1131580 and type 2 diabetes mellitus in a Han Chinese population

M.Y. Yu^{1,2*}, P.Q. Zhao^{1,3*}, X.H. Yan⁴, B. Liu¹, Q.Q. Zhang¹, R. Wang¹, C.H. Ma¹, X.H. Liang¹, F.L. Zhu¹ and L.F. Gao¹

¹Key Laboratory for Experimental Teratology of Ministry of Education, Shandong Provincial Key Laboratory of Infection & Immunology, Institute of Immunology, Shandong University School of Medicine, Shandong, China

²Department of Medicine, Binzhou Vocational College, Binzhou, Shandong, China

³Department of Clinical Laboratory, Zibo Central Hospital, Zibo, Shandong, China

⁴Shandong Medical College, Linyi, Shandong, China

*These authors contributed equally to this study.

Corresponding author: L.F. Gao

E-mail: glfflg@sdu.edu.cn

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ABSTRACT. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is expressed in different tissues and cells, including the pancreas and lymphocytes, and it can selectively induce apoptosis in tumor cells but not in most normal cells. TRAIL plays critical roles in type 1 diabetes mellitus, and is involved in type 2 diabetes mellitus (T2DM). We recently discovered the association of nonalcoholic fatty liver disease, a risk factor for T2DM, with a single nucleotide polymorphism (SNP) in the *TRAIL* (*TNFSF10*) gene at site 1595C/T (rs1131580), indicating the possible association of T2DM with this *TRAIL* polymorphism. The aim of this study was to investigate the

relationship of the *TRAIL* SNP at site 1595C/T (rs1131580) with T2DM susceptibility and the biometabolic parameters of T2DM in a Han Chinese population. The polymerase chain reaction-restriction fragment length polymorphism method was used to genotype SNP rs1131580 in 292 patients with T2DM and 266 healthy controls. We found that the frequency of the CC genotype and that of the C allele of rs1131580 were significantly higher in T2DM patients than in the control group. Additionally, the triglyceride and serum creatinine levels of T2DM patients with the CC genotype were significantly higher than those of patients with the TT genotype. Thus, the CC genotype of the *TRAIL* SNP at 1595C/T (rs1131580) confers increased susceptibility to T2DM in a Han Chinese population from Shandong Province. These data suggest that the CC genotype at this SNP is related to diabetic severity and it might be a candidate for the prognostic assessment of T2DM.

Key words: Tumor necrosis factor-related apoptosis-inducing ligand; Polymerase chain reaction-restriction fragment length polymorphism; Type 2 diabetes mellitus; Single nucleotide polymorphism

INTRODUCTION

Diabetes mellitus affects about 150 million people worldwide. The 2 most common forms of diabetes are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T2DM is the most common form of diabetes, accounting for 90 to 95% of all cases of diabetes worldwide (Zimmet et al., 2001). At present, T2DM is one of the most challenging health-care problems. The prevalence of T2DM has been increasing dramatically worldwide. China has the highest prevalence of diabetes in the world, and the incidence of diabetes is increasing rapidly, especially in urban areas (Villegas et al., 2006). Many factors, including obesity, hypertension, elevated cholesterol, and metabolic syndrome, increase the risk of developing T2DM. There is also a strong inheritable genetic component in T2DM (Freeman and Cox, 2006). T2DM is a chronic disease caused by the aberrant expression of many genes such as *TNF- α* , *TGF- β* , and *IL-1* (Wachlin et al., 2003; Hanley et al., 2006; Lin et al., 2009). In addition, it has been reported that hyperglycemic conditions induce the expression of apoptosis-regulatory genes by the renal tubular epithelium (Ortiz et al., 1997). Apoptosis can also be detected in renal biopsy samples from diabetic patients, suggesting a role for apoptosis-regulatory genes in diabetic pathogenesis (Kumar et al., 2004).

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), also known as Apo-2L, is a new member of the TNF superfamily. *TRAIL* was first identified by Wiley et al. (1995). *TRAIL* is expressed in different tissues and cells, including the pancreas and lymphocytes, and can selectively induce the apoptosis of tumor cells but not that of most normal cells. However, *TRAIL* is involved not only in apoptosis and immune regulation but also in vascular biology (Kavurma et al., 2008). Recently, *TRAIL* was suggested to be a potential new player in the pathogenesis of diabetes. *TRAIL* has been associated with both T1DM and T2DM (Corallini et al., 2007). However, *TRAIL* plays a dual role in diabetes depending on the type and the stage of the disease (Vaccarezza et al., 2007). Emerging evidence shows that *TRAIL*

plays critical roles in T1DM. *TRAIL* deficiency accelerates the development of autoimmune diabetes, while treatment with recombinant TRAIL ameliorates the severity of streptozotocin-induced T1DM (Lamhamedi-Cherradi et al., 2003; Zauli et al., 2010). In T2DM patients, the serum levels of TRAIL showed a tendency to decrease after insulin treatment, suggesting that TRAIL might be involved in diabetic vascular abnormalities by acting as an endogenous regulator of the vascular tone (Corallini et al., 2007). However, an association between single nucleotide polymorphisms (SNPs) in *TRAIL* (*TNFSF10*) and T2DM has not been reported. We previously found that the TT genotype of *TRAIL* at nucleotide 1595 was associated with a lower risk of fatty liver disease (FLD), which is related to the development and progression of T2DM (Yan et al., 2009). The aim of the current study was to evaluate the relationship of variants at nucleotide 1595 (rs1131580) in *TRAIL* to T2DM susceptibility and to biometabolic parameters in T2DM patients.

MATERIAL AND METHODS

Subjects

Two hundred and ninety-two patients with T2DM that fulfilled the new diabetes diagnostic criteria issued by the American Diabetes Association in 1997 and 266 healthy controls were recruited at the Shandong University affiliated Qilu Hospital and Zibo Central Hospital from January 2007 to January 2012. T2DM patients and healthy controls were from Shandong Province and all subjects were all ethnically Han. All recruited healthy controls were excluded from having autoimmune diseases. There were no significant differences in age or gender ratios between the 2 groups. This study was approved by the Medical Ethics Committee of Shandong University, and informed consent was obtained from all subjects before the study. The characteristics of the subjects are summarized in Table 1.

Table 1. Characteristics of type 2 diabetes mellitus (T2DM) patients and control subjects.

Subjects	T2DM (N = 292)	Normal (N = 266)
Age mean (years)	55.73 ± 8.54	53.73 ± 8.74
Gender (male/female)	156/136	139/127
Race	Chinese	Chinese
SBP (mmHg)	131.39 ± 12.62	-
DBP (mmHg)	84.03 ± 7.92	-
TC (mM)	4.64 ± 1.21	-
HDL (mM)	2.14 ± 1.02	-
LDL (mM)	3.02 ± 0.84	-
FPG (mM)	8.96 ± 2.55	-
GHbA1c (%)	8.43 ± 1.99	-
TG (mM)	2.42 ± 1.46	-
BUN (mM)	5.02 ± 2.83	-
SCr (μM)	81.42 ± 40.11	-

Values are reported means ± SD or N, unless otherwise stated. SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; FPG = fasting plasma glucose; GHbA1c = glycated hemoglobin A1c; TG = triglyceride; BUN = blood urea nitrogen; SCr = serum creatinine.

Detection of biometabolic parameters

Serum was separated following standard protocols and prepared for the detection

of biometabolic parameters. Briefly, we left the whole blood for 1 h at 37°C to allow it to clot, then centrifuged at 4000 rpm for 20 min at 4°C. The serum was collected and stored at -20°C. Biometabolic parameters including triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glycated hemoglobin A1c (GHbA1c), fasting plasma glucose (FPG), total cholesterol (TC), blood urea nitrogen (BUN), and serum creatinine (SCr) were detected in the sera of T2DM patients using conventional methods with a Beckman Coulter Automatic Biochemical Analyzer (USA) (Yang et al., 2012).

DNA extraction

Blood treated with anticoagulant was preserved at -20°C for genomic DNA extraction. Genomic DNA was extracted from whole blood using a leukocyte genomic DNA isolation kit (TIANGEN Bio-Engineering Co. Ltd., China) according to manufacturer instructions. The genomic DNA obtained was stored at -20°C for SNP analysis.

TRAIL genotyping

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for SNP genotyping. Specific primers were designed based on the *TRAIL* gene sequence and a previously published study (Gray et al., 2001). PCR was performed in a final volume of 25 µL with 100 ng DNA template, 2.5 µL 10X PCR buffer, 0.5 µL dNTPs, 10 pM forward primer (5'-aacatcttctgtctttataac-3') and reverse primer (5'-aaataaacagtactactgaag-3'), and 1.25 U Taq-DNA-polymerase (Takara, Japan). PCR cycling conditions were as follows: 94°C for 5 min, followed by 30 cycles of 94°C for 45 s, 48°C for 45 s, and 72°C for 45 s, with a final extension step at 72°C for 5 min. PCR products were digested with *TasI* at 65°C for 3 h. The digested products were checked by electrophoresis on 2.5% agarose gels and visualized by staining with ethidium bromide. The desired genotypes of *TRAIL* were confirmed by DNA sequencing in 2 randomly selected samples.

Statistical analysis

All data are reported as means ± SD. The genotype and allele frequencies were calculated manually and were found to follow Hardy-Weinberg equilibrium in both groups. The differences in genotype and allele frequencies between the 2 groups were analyzed by the chi-square test and the Fisher exact test, respectively. General linear regression analyses were used to calculate differences in quantitative traits among T2DM patients with different *TRAIL* genotypes and P values shown were adjusted for age and gender applying an additive genetic model. All data were analyzed with the GraphPad Prism 5.0 software (GraphPad Software, Inc., San Diego, CA, USA). A two-sided P value less than 0.05 was considered to indicate statistical significance.

RESULTS

Genotyping of the rs1131580 SNP in *TRAIL*

Consistent with our previous studies, 3 genotypes were identified at site 1595 in

TRAIL in all recruited subjects. Amplified PCR products were cut into 291- and 193-bp fragments (genotype CC) or 291-, 193-, 131-, and 62-bp fragments (genotype CT), or 291-, 131-, and 62-bp fragments (genotype TT) after digestion with *TasI* (Figure 1A). Each genotype was verified by DNA sequencing (Figure 1B).

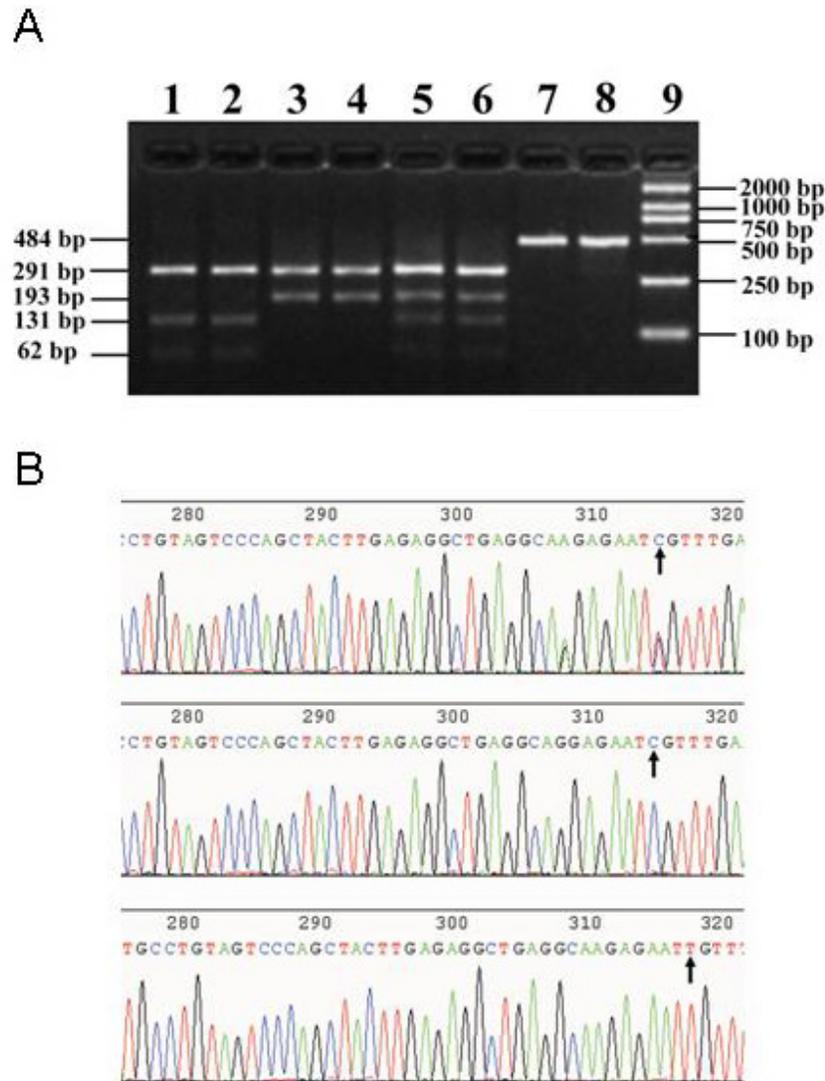


Figure 1. Genotyping of the *TRAIL* gene at site 1595 (rs1131580). PCR products and digestion products were electrophoretically separated on a 2.5% agarose gel and stained with ethidium bromide. Each genotype of *TRAIL* was verified by DNA sequencing. **A.** PCR products and restriction enzyme digestion by *TasI* in the 3'-UTR at position 1595. *Lanes 1 and 2* = TT genotype with 291-, 131- and 62-bp fragments; *lanes 3 and 4* = CC genotype with 291- and 193-bp fragments; *lanes 5 and 6* = CT genotype with 291-, 193-, 131- and 62-bp fragments; *lanes 7 and 8* = PCR products; *lane 9* = DL2 000 DNA marker. **B.** DNA sequencing of PCR products with the CT genotype (top panel), CC genotype (middle panel), or TT genotype (bottom panel) in the 3'-UTR at position 1595 (shown by arrows).

Genotype and allele frequencies of rs1131580 in T2DM patients and healthy controls

Based on the electrophoresis results, we determined and recorded the genotype of each individual and calculated the genotype and allele frequencies of this SNP manually. Genotype and allele frequencies of the SNP in the 2 groups were in Hardy-Weinberg equilibrium (control group: $\chi^2 = 1.7991$, $P = 0.4068$; T2DM group: $\chi^2 = 0.0078$, $P = 0.9961$). The frequency of the CC genotype was significantly higher in T2DM subjects than in healthy controls (T2DM group vs control group: 32.19 vs 25.94%, $P < 0.05$). Consistent with this result, the frequency of the C allele of SNP rs1131580 was significantly higher in the T2DM group than in the control group [T2DM group vs control group: 56.85 vs 48.87%, $P < 0.01$, OR = 1.378, 95% confidence interval (CI) = 1.088-1.745] (Table 2).

Table 2. Genotype and allele frequencies of *TRAIL* at site 1595 (rs1131580) in type 2 diabetes mellitus (T2DM) patients and healthy controls.

Group	N	Genotype frequency ^a , N (%)			P	Allele frequency ^b , N (%)		P
		CC	CT	TT		C	T	
T2DM	292	94 (32.19%)	144 (49.32%)	54 (18.49%)	0.0195	332 (56.85%)	252 (43.15%)	0.0083
Control	266	69 (25.94%)	122 (45.86%)	75 (27.82%)		260 (48.87%)	272 (51.13%)	

^aT2DM group vs control group, $P < 0.05$; ^bT2DM group vs control group, $P < 0.01$, OR = 1.378, 95%CI = 1.088-1.745.

Levels of biometabolic parameters in T2DM patients with different *TRAIL* genotypes

T2DM patients were classified into 3 groups according to their genotypes (CC, CT, or TT) at site 1595 in *TRAIL*, and the levels of biometabolic parameters in these groups were analyzed. The results indicated that the levels of TG and SCr in T2DM patients with genotype CC (TG: 2.57 ± 1.88 mM; SCr: 91.11 ± 64.45 μ M) were significantly higher than those of T2DM patients with genotype TT (TG: 1.74 ± 0.86 mM; SCr: 76.16 ± 20.61 μ M). Although FPG levels in T2DM patients with the CC genotype (8.40 ± 2.51 mM) were significantly lower than those of patients with the CT genotype (9.32 ± 2.54 mM), no differences in FPG levels were found between patients with the CC (8.40 ± 2.51 mM) and TT genotypes (8.98 ± 2.52 mM). TC, HDL, LDL, GHbA1c, and BUN showed no significant differences in T2DM patients with different *TRAIL* genotypes (Table 3).

Table 3. Comparison of general data and biometabolic parameters in type 2 diabetes mellitus patients with different genotype of *TRAIL* (rs1131580) (means \pm SD).

Items	CC (N = 94)	CT (N = 144)	TT (N = 54)	P
TC (mM)	4.65 \pm 1.08	4.60 \pm 1.33	4.73 \pm 1.10	0.7761
HDL(mM)	2.05 \pm 1.04	2.24 \pm 1.01	2.01 \pm 0.99	0.0899
LDL(mM)	3.03 \pm 0.85	3.00 \pm 0.85	3.07 \pm 0.82	0.8580
FPG (mM)	8.40 \pm 2.51	9.32 \pm 2.54	8.98 \pm 2.52	0.0227 [▲]
GHbA1c (%)	8.19 \pm 2.10	8.60 \pm 2.01	8.41 \pm 1.70	0.2800
TG (mM)	2.57 \pm 1.88	2.57 \pm 1.25	1.74 \pm 0.86	0.0006 [▲]
BUN(mM)	5.49 \pm 4.50	4.85 \pm 1.52	4.65 \pm 1.26	0.1233
SCr (μ M)	91.11 \pm 64.45	77.06 \pm 18.00	76.16 \pm 20.61	0.0166 [▲]

[▲] $P < 0.05$. For abbreviations, see legend to Table 1.

DISCUSSION

T2DM is a complex polygenic disease influenced by environmental and genetic factors. Over 30 T2DM susceptibility loci with different effect sizes have been identified and replicated by genetic association studies, and several genome-wide association scans for T2DM have also been carried out recently (Sladek et al., 2007; Unoki et al., 2008; Rung et al., 2009; Langberg et al., 2012). It has been reported that a functional polymorphism in the *TNF- α* gene, a long-standing T2DM candidate gene, is associated with T2DM and that a genetic polymorphism in the *TNF- α* promoter at site -308G/A is associated with diabetes and T2DM in the elderly (Chui et al., 2007; Susa S et al., 2008). However, emerging evidence from large-scale association analyses shows that the majority of common variation in the *TNF/LTA* gene region is not related to T2DM (Zeggini et al., 2005; Boraska et al., 2010). Plasma fatty acid concentration and distribution are closely linked to the development and progression of T2DM. SNPs in the TNF superfamily member *10b* (*TNFRSF10B*) gene, which encodes a receptor for TRAIL, appear to play a key role in fatty acid metabolism, suggesting a correlation between *TNFRSF10B* functional variants and T2DM risk (Voruganti et al., 2010). However, the relationship of TRAIL, a new member of the TNF superfamily, with T2DM remains unclear.

There are several SNPs in *TRAIL*, including 4 SNPs in the 5'-regulatory region, 2 SNPs within exons, and 5 SNPs in the 3'-untranslated region (3'-UTR) (Unoki et al., 2000; Wang et al., 2000; Gray et al., 2001). Generally, 3'-UTR has wide-range influences on gene regulation (Zhang et al., 2004; Watanabe et al., 2007). The polymorphism at position 1595 of *TRAIL* (rs1131580) was found to be associated with multiple sclerosis susceptibility in Japanese patients (Kikuchi et al., 2005). We also found that the TT genotype at nucleotide 1595 in *TRAIL* engendered a lower risk of FLD and a less severe form of steatosis in FLD patients in a Chinese population (Yan et al., 2009). Recently, the *TRAIL* SNP rs1131532 was identified as a possible prognostic factor for survival in patients operated on for invasive breast cancer (Jung et al., 2010). In addition, a promoter SNP in *TRAIL* was shown to functionally modulate the role of *TRAIL* in breast cancer pathogenesis (Pal et al., 2011). We also evaluated 4 SNPs in the promoter region of *TRAIL*. However, no SNPs were identified in a Chinese population at sites -707, -665, -597 of *TRAIL*, and genotype and allele frequencies at -621 showed no significant differences between non-alcoholic or alcoholic FLD patients and healthy controls. Since the 3'-UTR may be involved in gene regulation, the variant of *TRAIL* at site 1595 (rs1131580) likely influences *TRAIL* gene expression by changing a potential microRNA binding sequence, suggesting that it is a functional mutant. In our previous study, we found that SNP rs1131580 in *TRAIL* was correlated with FLD susceptibility in a Han Chinese population. Therefore, we selected this 3'-UTR SNP for our current study.

Our results in this study are consistent with those of our previous report in that 3 genotypes were found at site 1595 in *TRAIL* in the study subjects (Yan et al., 2009). In the present study, we found that the CC and CT genotypes at rs1131580 were more commonly found in T2DM patients than the TT genotype. The frequency of the CC genotype was also significantly higher in the T2DM group than in the control group as was the frequency of the C allele, suggesting that the CC genotype at rs1131580 might confer susceptibility to T2DM together with other risk factors. This result is consistent with the fact that nonalcoholic fatty liver disease is a risk factor for T2DM (Fan et al., 2007; Arase et al., 2009). Consistent with our previous study on fatty liver diseases, TG levels in T2DM patients with the CC genotype were significantly

higher than those of patients with the TT genotype. Since TG is an independent risk factor for many T2DM-associated complications and coexisting liver diseases are a risk factor for the development of T2DM (Wanner and Krane, 2011), the CC genotype of site 1595 in *TRAIL* might be associated with the severity of diabetes. However, the role of TRAIL in T2DM has not been investigated so far. Serum TRAIL levels were associated with carotid intima-media thickness in a subset of T2DM patients with macrovascular diseases (Kawano et al., 2011). In addition, the serum concentrations of TRAIL and osteoprotegerin, the endogenous decoy receptor of TRAIL, in T2DM patients with microalbuminuria and macroalbuminuria are significantly higher than those of patients with normoalbuminuria, and serum osteoprotegerin was identified to be an independent factor associated with the severity of diabetic nephropathy (Chang et al., 2011). In this study, we also detected higher levels of Scr in T2DM patients with the CC genotype, further indicating that patients with the CC genotype at SNP rs1131580 of *TRAIL* might have more severe T2DM than patients with the TT genotype.

In summary, our results demonstrate that genotype CC at site 1595 of the *TRAIL* gene engenders a higher risk for T2DM and a more severe form of T2DM. We speculate that this potentially functional polymorphism in the *TRAIL* gene might be a good candidate for T2DM diagnosis and prognosis. However, further studies are needed to analyze the association of TRAIL polymorphisms with other aspects of T2DM, such as insulin resistance and β cell dysfunction, to clarify the role of the *TRAIL* polymorphism rs1131580 in T2DM pathogenesis. Additionally, due to the sample size of this study, a large-scale association analysis of *TRAIL* gene functional variants and T2DM risk is necessary to validate these results.

Conflicts of interest

We declare no conflict of interests.

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