Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

The association between PAI-1 -675 4G/5G polymorphism and type 2 diabetes mellitus

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Received March 28, 2017; **Accepted** May 19, 2017; **Published** August 15, 2017

Doi: http://dx.doi.org/10.14715/cmb/2017.63.7.11

Abstract: In this study, we aimed to analyze the association between plasminogen activator inhibitor 1 (PAI-1) -675 4G/5G polymorphism and type 2 diabetes mellitus (T2DM) risk. We included in 187 T2DM patients and 186 heathy controls between 2014 and 2017 from Tianjin Gong An Hospital, China. All patients and controls were ethnically Chinese Han population. The primers and polymerase chain reaction (PCR) conditions were performed. Results from this case-control study suggested that PAI-1 -675 4G/5G polymorphism was not associated with T2DM risk in four genetic models. Additionally, PAI-1 -675 4G/5G polymorphism was not associated with clinical and laboratory characteristics, such as age, gender, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and HbA1c. In conclusion, this case-control study suggested that PAI-1 -675 4G/5G polymorphism was not associated with T2DM risk in this population.

Key words: Type 2 diabetes mellitus; PAI-1; Polymorphism; Association.

Introduction

Type 2 diabetes mellitus (T2DM) is a main contributor for death, disability, and rising medical expenses in both developed countries and developing countries (1). International Diabetes Federation (IDF) in 2015 reported India as the territory with second highest number of adults with diabetes, 69.2 million, behind China. T2DM is linked with obesity and the development of significant comorbidities, such as liver, heart and kidney disorders (2).

Plasminogen activator inhibitor 1 (PAI-1) is an important constituent of the fibrinolytic system. Yarmolinsky et al. supported a link between PAI-1 and T2DM, independent of established diabetes risk factors (3). Al-Hamodi et al. suggested that PAI-1 activity was higher in subjects with T2D with metabolic syndrome and non-diabetic subjects with metabolic syndrome (4). Nagi et al. found thatrRaised PAI-1 activity may play an important role in the pathogenesis of macrovascular disease in subjects with NIDDM (5). A number of DNA polymorphisms have previously been identified in the gene, including a G insertion at position −675 (6). Previous study suggested that homozygous carriers of the 4G allele have higher PAI-1 than subjects with the 5G allele (7). In this study, we aimed to analyze the association between PAI-1 -675 4G/5G polymorphism and T2DM risk.

Materials and Methods

Study subjects

We included in 187 T2DM patients and 186 heathy controls between 2014 and 2017 from Tianjin Gong An Hospital, China. All patients and controls were ethnically Chinese Han population. The controls were randomly selected from healthy individuals who underwent routine physical examination. Information on individuals was gathered from both T2DM patients and controls. The study protocol was approved by the Institutional Review Boards of the Tianjin Gong An Hospital.

Genotyping and quality control

The blood samples were collected from each enrolled subjects. Genomic DNA was prepared from leukocyte pellets by sodium dodecylsulfate lysis, ammonium acetate extraction, and ethanol precipitation. The primers and polymerase chain reaction (PCR) conditions were performed as previously described (8). A 99-bp PCR product was digested with Bsl I. The uncut product (99 bp) shows the presence of 4G allele. If the PCR product was cut into two fragments as 77 and 22 bp, it revealed the 5G allele. Ten percent of the samples were subjected to randomly repeat blind assays and all results were consistent.

Statistical analysis

All statistical analyses were performed by the Statistical Package for Social Sciences for Windows software (Windows version release 11.0; SPSS, Inc., Chicago, IL, USA). Results for all measurements are expressed as mean±standard deviation (SD) and median. The Kolmogorov-Smirnow test was used to formally evaluate the normality of distributions. The chi-square (χ^2) was performed to test for a comparison of differences in genotype frequencies among groups. Kruskal-Wallis and Dunn tests were evaluated to compare the groups. Hardy-Weinberg equilibrium (HWE) was also tested by a chi-square (χ^2) test. Differences were considered significant when $P<0.05$.

Results

The genotype and allele frequencies of PAI-1 -675 4G/5G polymorphism were shown in Table 1. The frequencies of 4G/4G, 4G/5G and 5G/5G genotypes in the T2DM patients were 34.8%, 51.9%, and 12.3% and were 35.5%, 50.0%, and 14.5% in the controls. Heterozygous (4G/5G) genotype and homozygous (5G/5G) were not associated with the risk of developing T2DM (P>0.05). The frequencies of 4G and 5G in the T2DM patients were 60.7%, 39.3% and were 60.4%, 39.6% in the controls. The 5G allele was not associated with the risk of T2DM (P>0.05). No significant result was found when the patients and controls were compared in recessive model and dominant model (P>0.05).

Clinical and laboratory characteristics of T2DM patients broken down in dominant model of PAI-1 -675 4G/5G polymorphism are shown in Table 2. Age, gender, and body mass index were similar among the patients carrying the 4G allele and patients with 5G/5G (P>0.05). In addition, systolic blood pressure and diastolic blood pressure were similar among the patients carrying the 4G allele and patients with 5G/5G (P>0.05). Furthermore, there was no difference in the levels of total cholesterol, triglycerides, and HbA1c.

Discussion

In this present case-control study, we assessed PAI-1 -675 4G/5G polymorphism and T2DM risk in a Chinese Han population. Results from this case-control study suggested that PAI-1 -675 4G/5G polymorphism was not associated with T2DM risk in four genetic models. Additionally, PAI-1 -675 4G/5G polymorphism was not associated with clinical and laboratory characteristics, such as age, gender, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and HbA1c. In a previous study, Prasad et al. also did not find a significant association between PAI-1 -675 4G/5G polymorphism and T2DM risk (9). Additionally, Meigs et al. concluded that the PAI-1 4G/5G polymorphism was not an important genetic risk factor for type 2 diabetes in this community-based sample (10). However, Zhao et al. suggested that PAI-1 4G/5G polymorphism may be associated with T2DM development in a meta-analysis (11). The main reason might be the small sample size. Thus, more case-control studies with large sample size are needed to confirm our results.

Benyamin et al. suggested that PAI-1 activity was significantly higher in prediabetic subjects than those with NGT; and there was a significant association between glycemic status in prediabetic subjects and PAI-1 activity (12). Kodaman et al. suggested that body mass index, triglycerides, and fasting glucose were strongly correlated with PAI-1 (13). Canecki-Varžić et al. found that elevated PAI-1 levels are associated with higher BMD in obese diabetic patients (14). Xu et al. indicated that PAI-1 4G/5G polymorphism was associated with the development and progression of predominant proteinuria diabetes nephropathy (15).

This study had some limitations. First, this was a case-control study. Therefore, we cannot exclude selec-

Table 1. Genotype and allele frequencies of PAI-1 -675 4G/5G polymorphism in T2DM patients and healthy controls.

	T2DM case (%)	Healthy control (%)	*P* value
Genotype			
4G/4G	65 (34.8%)	66 (35.5%)	
4G/5G	97 (51.9%)	93 (50.0%)	>0.05
5G/5G	25 (13.3%)	27 (14.5%)	>0.05
Allele			
4G	227 (60.7%)	225 (60.4%)	
5G	147 (39.3%)	147 (39.6%)	>0.05
Recessive model			
4G/4G	65 (34.8%)	66 (35.5%)	
4G/5G+5G/5G	122 (65.2%)	120 (64.5%)	>0.05
Dominant model			
4G/4G+4G/5G	162 (86.7%)	159 (85.5%)	
5G/5G	25 (13.3%)	27 (14.5%)	>0.05

Table 2. Clinical and laboratory characteristics of T2DM patients with PAI-1 -675 4G/5G polymorphism.

Characteristics	4G/5G+4G/4G	5G/5G	*P* value
Age (years)	58.5±11.2	61.2±10.1	>0.05
Gender (% male)	54	57	>0.05
BMI (Kg/m^2)	25.7±12.3	26.5±10.2	>0.05
Systolic BP (mm/Hg)	144±22.5	149±27.6	>0.05
Diastolic BP (mm/Hg)	89.2±12.6	92.3±15.1	>0.05
Total cholesterol (mmol/L)	5.5±1.6	5.2±1.3	>0.05
Triglycerides (mmol/L)	2.2±2.6	2.8±2.1	>0.05
HbA1c (%)	8.7±1.2	8.9±1.1	>0.05

BMI, body mass index; BP, blood pressure.

tion bias. Second, only one gene polymorphism was investigated in this study. Third, other clinical factor and lifestyle were not considered in this study. Fourth, the results should be reinforced by additionally functional data. Finally, the sample size of this study was small. Thus, more studies are needed to confirm the results of this study.

In conclusion, this case-control study suggested that PAI-1 -675 4G/5G polymorphism was not associated with T2DM risk in this population.

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