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The Role of rs1799889 Genetic Variation in Type 2 Diabetes and Diabetic Nephropathy Risk

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ABSTRACT

Objective: Type 2 diabetes mellitus (T2 DM) represents a complex metabolic disease with genetic heterogeneity and increasing worldwide prevalence. One of the candidate genes associated with T2 DM and diabetic nephropathy (DN) is the plasminogen activator inhibitor-1 (PAI-1) gene. The present research aimed to reveal the polymorphism frequencies of the PAI-1 gene 4G/5G and to investigate the role of this polymorphism in T2 DM and DN development.

Materials and Methods: The genomic DNA of the 261 individuals was included in this study. The polymerase chain reaction (PCR) method with 4G and 5G allele-particular primers was used to identify the polymorphism of PAI-1 4G/5G. The PCR products were evaluated using a CCD camera after 2% agarose gel electrophoresis.

Results: Although the frequencies of the gene genotypes differed statistically significant between 80 patients and 51 patients with and without DN, respectively, and the control group, no statistically significant difference was detected between those with and without DN. The 5G/5G genotype was found to be significantly higher in the patient group.

Conclusion: The findings suggest that there is a significant correlation between variants of the PAI-1 gene and the risk for T2 DM formation.

Keywords: Type-2 diabetes, diabetic nephropathy, PAI gene, rs1799889

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INTRODUCTION

Type 2 diabetes mellitus (T2 DM), the prevalence of which is gradually increasing in the world, is one of the metabolic diseases (1–3). T2 DM is a disease with genetic heterogeneity and complex interaction of genetic and environmental factors (2, 4). T2 DM is a chronic disease with macrovascular and microvascular complications. One of its microvascular complications is diabetic nephropathy (DN) (4–6). In DN, glomerular basement membrane thickening and extracellular matrix expansion surrounding mesangial cells occur (7). In addition to playing an inhibitory role in extracellular matrix degradation, PAI-1 also initiates diabetes-related complications (8, 9).

Increased PAI-1 expression also plays a significant part in the pathogenesis of DN since it may lead to the development of kidney disease by causing extracellular matrix (ECM) accumulation (10).

The PAI-1 gene (accession No. P05121) is located on chromosome 7 (q 21.3–q 22), spans 12.3 kb of DNA, and contains 9 exons and 8 introns (10–13). The 4G/5G (rs1799889) polymorphism is located in the PAI-1 gene promoter region and is caused by the insertion/deletion variation of guanosine that is located 675 bases upstream from the gene's transcriptional starting point (11).

In recent years, many studies have indicated the relationship between the rs1799889 polymorphism of the PAI-1 gene and the risk of diabetes and diabetic complications, by primarily concentrating on diabetic coronary artery disease, DN, and diabetic retinopathy (DR) (8, 9, 12–15).

In light of all this information, the current research aimed to identify the frequency of the PAI-1 rs1799889 polymorphism and examine its role in T2 DM and DN in the Eastern Black Sea population.

MATERIALS and METHODS

Demographic and clinical variables (e.g., age, BMI, duration of diabetes, gender, smoking, DR, hypertension and family history) were recorded for all cases. This study included 131 patients [80 patients without DN (DN^-) and 51 with DN (DN^+)] and 130 controls recruited from the Department of Internal Medicine of Artvin State Hospital. Approval for the current research was acquired from the local ethics committee of Karadeniz Technical University (date: 05.03.2014; number: 2013/134).

Table 1. Clinical characteristics of the control group, without diabetic nephropathy (DN^-) group and with diabetic nephropathy (DN^+) group

	DN^- n %		DN^+ n %		Control n %		Statistics
	-	+	-	+	-	+	
Gender (M/F)	25/55		28/23		44/86		0.012*
	31.3/68.8		54.9/45.1		33.8/66.2		
Smoking	72	8	44	7	127	3	0.514*
	90	10	86.3	13.7	97.7	2.3	
Diabetic retinopathy	55	25	33	18	130	0	0.631*
	68.8	31.3	64.7	35.3	100	0	
Hypertension	38	42	19	32	122	8	0.249*
	47.5	52.5	37.3	62.7	93.8	6.2	
Family history	40	40	24	27	120	10	0.743*
	50	50	47.1	52.9	92.3	7.7	

*: Pearson Chi-Square Tests (n-%)

Table 2. Distribution of PAI-1 gene and allele frequencies in total patients, control and Type 2 diabetic patients with nephropathy (DN^+) or without nephropathy (DN^-)

PAI-1	Control (n=130) n (%)	T2DM (n=131) n (%)	p	OR (95%CI)	DN^- (n=80) n (%)	DN^+ (n=51) n (%)	p	OR (95%CI)
Genotype								
4G/4G	44 (34)	33 (25)		Reference	18 (22.5)	15 (29.4)		Reference
4G/5G	44 (34)	16 (12)	0.049	0.485 (0.234–0.004)	11 (13.8)	5 (9.8)	0.342	0.545 (0.154–1.922)
5G/5G	42 (32)	82 (63)	0.001	2.60 (1.450–0.671)	51 (63.8)	31 (60.8)	0.449	0.729 (0.322–1.652)
Alleles								
4G	132 (50.3)	82 (31)	4.176	Reference	47 (29)	35 (34)	0.400	Reference
5G	126 (49.7)	180 (69)		2.299 (1.608–0.287)	113 (71)	67 (66)		0.796 (0.467–1.355)

*: Pearson Chi-square Test; CI: Confidence interval; OR: Odds ratio

Genomic DNA was isolated using the DNA isolation Kit (EZ-10 Spin Colon Blood Genomic DNA Minipreps Kit, Biotechnology Department Bio Basic Inc., Markham, Ontario, Canada). PCR was performed using the following primers (for the 4G allele: 5' - GTC TGG ACA CGT GGG GA- 3'; for the 5G allele: 5' - GTC TGG ACA CGT GGG GG- 3'; Downstream primer: 5' - TGC AGC CAG CCA CGT GAT TGT CTA G- 3'; Upstream primer: 5'- AAG CTT TTA CCA TGG TAA CCC CTG GT- 3') (Integrated DNA Technologies Inc., Leuven, Belgium) and the PCR mixture containing 50 µg genomic DNA, 1XPCR buffer, 0.2 mM dNTP mixture, 50 pmol allele-specific primers, 50 pmol common downstream primer, 2.5 pmol control upstream primer, and 25 U Taq polymerase in a 25 µl total volume (11). The following cycling conditions were set: the pre-denaturation step of 3 min at 94°C, denaturation of 35 cycles of 1 min at 94°C, annealing of 1 min at 54°C, and the extension step of 1 min at 72°C, followed by the single-cycle final extension step at 72°C for five min, using a Thermal Cycler T100 (Bio-Rad, Foster City, CA, USA).

The amplified PCR products were run in a 2% agarose gel and then imaged with a CCD camera after the execution and the values were analyzed using the gel analysis software (LabWorks, Cambridge, UK). The genotyping and classification of the samples into one of the three potential genotypes 5G/5G, 4G/4G, or heterozygous 4G/5G were carried out. The homozygous 4G genotype was determined based on the PCR result that gave a 139-bp band only with the 4G primer but not with the 5G primer. The homozygous 5G genotype was determined based on the PCR result that gave a 139-bp band only with the 5G primer but not with the 4G primer. The heterozygous 4G/5G genotype was determined based on the PCR result that gave a 139-bp band with the 4G and 5G primers.

Statistical Analysis

In this study, all data were statistically analyzed using the SPSS ver.21 software. Pearson chi-square test was conducted for the analysis of some individual characteristics of controls and patients. The Mann-Whitney Rank Sum test was used to analyze some biochemical properties of the control and patient groups. According

Table 3. Some biochemical characteristics of total patients, control and Type 2 diabetic patients with nephropathy (DN^+) or without nephropathy (DN^-)

		n	Mean±SD	Median (25%–75%)
Age	DN^-	80	57.45±11.71	58.50 (48.00–66.75)
	DN^+	51	63.01±13.79	63.00 (53.00–73.00)
P			0.021**	
	Control	130	57.50±16.26	55.00 (48.00–69.00)
	Total patients	131	59.61±12.80	61.00 (50.00–68.00)
P			0.187**	
BMI	DN^-	80	31.63±5.73	31.23 (27.34–34.64)
	DN^+	51	30.98±5.57	29.75 (26.37–36.32)
P			0.605**	
	Control	130	26.84±5.15	26.29 (22.39–30.81)
	Total patients	131	31.38±5.66	31.14 (27.05–34.88)
P			0.000**	
Duration of diabetes	DN^-	80	5.77±4.75	5.00 (2.00–8.00)
	DN^+	51	9.01±7.84	7.00 (2.00–15.00)
P			0.041**	
	Control	130	0.00±0.00	0 (0–0)
	Total patients	131	7.05±6.32	5.00 (2.00–10.00)
P			0.000**	
HbAC1	DN^-	80	7.95±8.06	6.75 (5.80–7.40)
	DN^+	51	6.78±1.78	6.60 (5.00–7.60)
P			0.468**	
	Control	130	6.87±6.46	6.10 (5.70–6.35)
	Total patients	131	7.50±6.41	6.70 (5.50–7.50)
P			0.003**	
Creatin	DN^-	80	0.70±0.10	0.69 (0.62–0.77)
	DN^+	51	1.73±1.94	1.04 (1.00–1.44)
P			0.000**	
	Control	130	0.76±0.27	0.73 (0.58–0.85)
	Total patients	131	1.10±1.30	0.78 (0.66–1.00)
P			0.019**	
Cholesterol	DN^-	80	208.37±56.25	196.50 (172.25–241.50)
	DN^+	51	181.41±43.28	176.00 (158.00–200.00)
P			0.007**	
	Control	130	180.09±40.09	178.00 (159.50–201.00)
	Total patients	131	197.87±53.08	187.00 (162.00–226.00)
P			0.075**	
HDL	DN^-	80	45.02±13.06	45.00 (34.70–53.07)
	DN^+	51	41.23±13.66	41.80 (33.00–45.00)
P			0.058**	
	Control	130	48.10±19.67	47.90 (36.90–58.70)
	Total patients	131	43.54±13.37	43.00 (34.00–51.00)
P			0.035**	
LDL	DN^-	80	125.42±45.90	118.00 (96.25–154.50)
	DN^+	51	117.35±37.82	110.00 (91.00–150.00)
P			0.325**	
	Control	130	112.23±37.22	111.00 (91.00–128.00)
	Total patients	131	122.28±42.96	112.00 (94.00–150.00)
P			0.240**	
Triglyceride	DN^-	80	188.70±125.54	154.50 (109.25–251.25)
	DN^+	51	167.70±98.75	150.00 (96.00–210.00)
P			0.394**	
	Control	130	137.92±73.74	117.00 (86.00–198.00)
	Total patients	131	180.52±115.90	150.00 (108.00–229.00)
P			0.002**	

SD: Standard deviation; **: Mann-Whitney Rank Sum Test. Median (25%-75%)

Table 4. Distribution of PAI-1 Gene 4G/5G polymorphism genotypes according to some clinical parameters of controls and patients

Parameters	Group	Genotypes		
		4G/4G n	4G/5G n	5G/5G n
Number	Total patients	33	16	82
	Control	44	44	42
HbA1C (%)	Total patients	8.60±1.75	9.13±2.73	6.73±0.15
	Control	8.40±2.36	6.06±0.09	6.12±0.10
Statistics		p*=0.943	p*=0.421	p=0.523
Cholesterol (mg/dl)	Total patients	199.79±9.92	212.56±11.16	194.25±0.15
	Control	180.81±5.94	187.55±10.15	171.52±9.27
Statistics		p*=0.154	p*=0.045	p*=0.018
Triglycerides (mg/dl)	Total patients	185.63±16.12	161.93±20.02	182.10±14.35
	Control	140.63±14.07	134.86±15.72	138.28±18.37
Statistics		p*=0.040	p*=0.018	p*=0.066
Systolic pressure	Total patients	135.15±4.01	140.00±5.84	136.34±2.39
	Control	123.63±1.40	117.27±2.29	120.95±3.01
Statistics		p*=0.010	p*=0.000	p*=0.003
Diastolic pressure	Total patients	80.30±2.06	79.37±2.13	81.10±1.66
	Control	71.36±1.77	70.90±1.72	69.04±2.05
Statistics		p*=0.003	p*=0.004	p*=0.001
Creatine	Total patients	0.89±0.28	1.57±2.44	1.10±1.25
	Control	0.71±0.18	0.83±0.37	0.77±0.25
Statistics		p=0.036	p=0.626	p=0.226
HDL	Total patients	44.76±15.46	46.23±13.66	42.54±12.46
	Control	49.27±14.80	51.75±27.09	43.06±13.96
Statistics		p=0.067	p=0.595	p=0.487
LDL	Total patients	128.42±47.32	135.56±45.34	117.22±40.27
	Control	112.64±36.95	114.59±39.04	109.33±37.22
Statistics		p*=0.194	p=0.169	p=0.731

p*: Independent two sample t-test

to the genotypes, the analysis of the biochemical properties of the patient and control groups was carried out by the independent two-sample t-test. The comparison of controls, T2 DM patients, DN^+ and DN^- were performed using Pearson's chi-square test according to the distribution of genotypes. The Shapiro-Wilk test was used for the normality test. P-values below 0.05 were considered statistically significant.

RESULTS

Some individual features of the control group, DN^- and DN^+ patients are shown in Table 1. Gender (p:0.012), smoking (p:0.514), diabetic retinopathy (p:0.631), hypertension (p:0.249) and family history (p:0.743) were not found to differ significantly in T2 DM and diabetic nephropathy compared to the control group.

The distributions and allele frequencies of the PAI-1 gene in T2 DM and DN patients are shown in Table 2. In this research, we found the genotype frequencies of the PAI-1 rs1799889 polymorphism to be 34% 4G4G, 34% 4G5G, and 32% 5G5G in the control group and 25% 4G4G, 12% 4G5G, and 63% 5G5G in the patient group. The PAI-1 4G5G genotype was determined to differ statistically significantly between the control group and T2 DM patients (p:0.001). The 5G5G genotype was observed to be significantly higher in the patient group. We found the genotype frequencies of PAI-1 rs1799889 polymorphism to be 22.5% 4G4G, 13.8% 4G5G, and 63.8% 5G5G for DN^- patients and 29.4% 4G4G, 9.8% 4G5G, and 60.8% 5G5G for the DN^+ patients. The difference in genotype frequencies between the T2 DM patients without nephropathy and with nephropathy was not statistically significant (p:0.449).

Some biochemical characteristics of controls, T2DM patients, DN^- and DN^+ patients are demonstrated in Table 3. Accordingly, creatine and cholesterol were statistically different among DN^- with DN^+ patients (p:0.000, p:0.007, respectively). The age of DN^+ was statistically lower in comparison with that of DN^-. There were no

significant differences between DN^- and DN^+ concerning the duration of diabetes (p=0.041), BMI (p:0.605), HbA1c (p:0.468), HDL (p:0.058), LDL (p:0.325) and triglyceride (p:0.394). No statistical differences were obtained between patients and controls with regard to age (p:0.187), Cholesterol (p:0.075) and LDL (p:0.240).

No significant differences were determined between the patient and control groups concerning BMI (p:0.000), the duration of diabetes (p:0.000), HbA1c (p:0.003), creatinine (p:0.000), HDL (p:0.035), and triglyceride (p:0.002).

The distribution of some clinical parameters, according to genotypes, is presented in Table 4 for controls and patients. No statistically significant difference according to genotypes was detected regarding HDL, LDL, and HbA1C value. Furthermore, a statistically significant difference was detected concerning cholesterol in the 4G5G (p:0.045) and 5G5G (p:0.018) genotypes. Concerning triglyceride, a statistically significant difference was revealed in the 4G4G (p:0.040) and 4G5G (p:0.018) genotypes. In terms of creatinine, a statistical difference was determined in the 4G4G (p:0.036) genotype. In terms of systolic and diastolic pressure, a statistically significant difference was detected in all genotypes (p-values for systolic pressure; 4G4G: 0.010, 4G5G: 0.000, 5G5G: 0.003 and p-values for diastolic pressure; 4G4G: 0.003, 4G5G: 0.004, 5G5G: 0.001, respectively).

DISCUSSION

The findings obtained in this study showed that the gender, smoking, diabetic retinopathy, hypertension, and the family history rates of T2 DM patients with or without nephropathy were not significantly different from those of the control group. Consistent with our findings, another study reported no significant differences in T2 DM patients with or without nephropathy concerning age, gender, and BMI (6).

In our study, when each patient and control group was analyzed for the genotype distribution and allele frequency of PAI-1 4G5G, the genotype frequency was determined to be 4G4G 34%, 4G5G 34% and 5G5G 32% for the control group, and as 4G4G 25%, 5G5G 63% and 4G5G 12% for all patients. A statistically significant difference was determined between the groups concerning the frequency of genotypes.

In our study, when DN^- and DN^+ groups were analyzed concerning the genotype distribution and allele frequency of PAI-1 4G5G, no statistically significant differences were detected. Many studies have indicated inconsistent findings on the significance of the PAI-1 rs1799889 polymorphism as a genetic risk indicator of diabetic nephropathy or retinopathy (8, 16). Xue et al. (10) determined that the PAI-1 gene could be associated with the risk of DN of the 4G4G genotype. Xu et al. (7) concluded that the PAI-1 rs1799889 polymorphism was related to DN development and progression. In a meta-analysis study, Zhao argued that the PAI-1 rs1799889 polymorphism could be related to T2 DM development (12). Saely et al. (17) studied the PAI-1 rs1799889 polymorphism in T2 DM subjects and suggested that this polymorphism was related to T2DM.

In a few studies conducted on DN patients, researchers have reported that the PAI-1 rs1799889 polymorphism is related to DN (4, 7). Chang et al. (4) stated that the homozygous 5G allele in the PAI gene rs1799889 polymorphism was defined as a protective factor in the development of diabetes in obese diabetic and insulin resistance patients. In a meta-analysis study, it was shown that the PAI-1 4G allele could be a risk allele for DN sensibility in the Chinese population (18). Unlike our results, Chen et al. (19) reported that the PAI-1 rs1799889 polymorphism was not associated with T2 DM risk.

CONCLUSION

In the literature review, it was observed that different results were presented in different populations regarding the relationship between this gene and T2 DM and DN. This may arise from the limited knowledge about heterogeneity in populations and the underlying mechanism. To our knowledge, no studies have been conducted on T2 DM and DN and the PAI-1 rs1799889 polymorphism in our country. In a population, it may be essential to determine which polymorphic variants are most important concerning disease development and treatment and to make haplotype maps in different populations. Accordingly, the PAI-1 gene in the Eastern Black Sea Turkish population is associated with the rs1799889 polymorphism T2 DM, and this polymorphism can be used as a genetic biomarker of T2 DM in the Eastern Black Sea Turkish population.

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Conflict of Interest: The authors have no conflict of interest to declare.

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