P-0681- Genetic Association of APOA5 Gene Variant with Diabetic Nephropathy

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Background: Type 2 Diabetes Mellitus (T2D), characterized by higher circulating glucose levels or insulin insufficiency, is associated with metabolic dysregulations (obesity, hypertension, dyslipidemia etc) with strong environmental and genetic influences (1). T2D is also considered as one of the major risk factor of vascular diseases thus severely compromising the life expectancy. Diabetic nephropathy (DN), a micro vascular complication, affects normal functioning of kidneys in diabetic patients and one of the leading causes of kidney failures (2). Due to high genetic susceptibility of South Asian populations including Pakistanis towards T2D, it could be predicted that they are genetically predisposed to the risk of DN. Apolipoprotein A5 (APOA5) is an important member of gene cluster regulating lipid metabolism. A genetic variant in the promoter region of APOA5 (-1131T>C, rs662799) associates with hyperlipidemia and thus could also contribute to DN (3).

Study Aim: To explore association of rs662799 variant with DN in Pakistani subjects.

Methods: Total 348 individuals of Pakistani ancestry were categorized into three study groups; non-diabetic, non-nephropathic (NDNN), diabetic non-nephropathic (DNN), and diabetic nephropathic (DN). The anthropometric and clinical data were collected. The rs662799 variant (T/C alleles) based genotyping of all study groups was performed through Restriction Fragment Length based Polymerase Chain Reaction (PCR-RFLP) assay using Tru1I (MseI) restriction enzyme. The statistical correlations were explored using SPSS package.

Results & Discussion: Frequency of the minor C allele of rs662799 variant did not change much (28-31%) in three study groups but homozygous C/C genotype frequency was slightly raised in DN (25%) as compared to NDNN and DNN groups (Table 1). No significant association of C allele found with DN (Table 2). Levels of all clinical variables were raised in DN groups compared to NDNN and DNN (Table 3). The C allele showed mild yet significant association with elevated triglyceride levels (Table 4).

Table 1: Allele and genotype frequencies of rs662799 variant

Alleles	Frequencies (Proportions) in Study Groups		
	NDNN	DNN	DN
T	0.72	0.69	0.70
C	0.28	0.31	0.30
Genotypes			
T/T	0.61	0.60	0.65
T/C	0.22	0.17	0.10
C/C	0.17	0.22	0.25

Table 2 : Association of rs662799 variant genotypes with disease status

Genotypes	NDNN vs DNN		NDNN vs DN		DNN vs DN	
	OR (95%CI)	p-valve	OR (95%CI)	p-valve	OR (95%CI)	p-valve
TT vs TC	0.80 (0.36-1.78)	0.61	**0.43 (0.22-0.87)**	**0.016**	0.54 (0.22-1.35)	0.4
TT vs CC	1.30 (0.61-2.79)	0.61	1.33 (0.74-2.39)	0.16	1.03 (0.48-2.18)	0.4
TT vs TC+CC	0.78 (0.47-1.31)	0.35	0.61 (0.35-1.05)	0.07	1.29 (0.70-2.38)	0.6

Table 3: rs662799 variant genotypes based levels (Means ± SD) of clinical variables in study groups

Genotypes		NON-DIABETIC NON-NEPHROPATHY (NDNN)						DIABETIC NON-NEPHROPATHY (DNN)						DIABETIC NEPHROPATHY (DN)					
		TG mg/dl	HDL mg/dl	Chol mg/dl	LDL mg/dl	UCR	BUN mg/dl	TG mg/dl	HDL mg/dl	Chol mg/dl	LDL mg/dl	UCR	BUN mg/dl	TG mg/dl	HDL mg/dl	Chol mg/dl	LDL mg/dl	UCR	BUN mg/dl
T/T	Mean	132	36.5	182.3	119.5	25.3	19.9	191.2	37.8	172	133.8	30	27.8	212.4	34.5	205	156.9	31.7	34
	S.D	30.2	6.3	31.3	25.5	15.7	6.5	56	9.5	37.7	11.8	16.1	6.5	48	9.7	34.9	20.6	27.7	16.1
C/T	Mean	138.8	36.6	173	118.7	29.2	19.6	172.6	34.5	153.1	127	34.2	30.2	219.6	33.9	203.9	158.6	38.8	44.2
	S.D	36.5	7.7	38.6	32.2	10.8	6	24.9	5	19	8.9	28.1	8.5	32.5	6.5	26.4	29.3	23.3	28.1
C/C	Mean	137.3	37.5	187	122.1	24.3	23.3	190.6	38.1	165.5	134.7	36.4	39.3	226.8	32.8	191.7	159.7	39.2	36.4
	S.D	34.9	6.9	34.3	29.4	13.3	5.2	50.1	10	32.6	8.9	26.8	5.8	28.9	5.8	21.3	30.3	25.3	26.8

Table 4: Association of rs662799 variant's C allele with risk variables in three study groups

Risk Variables	Association of risk variables with disease status β-Coefficients (95% CI), p-values		
	NDNN	DNN	DN
Age (Years)	1 (0.91-1.01) 0.89	0.98 (0.99-1.04) 0.58	0.988 (0.95-1.02) 0.17
BMI (Kg/m²)	1.06 (0.46-2.44) 0.081	0.93 (0.335-2.5) 0.088	2.5 (0.76-7.8) 0.017
Dyslipidemia (mg/dL)	0.98 (0.929-1.04) 0.25	0.93 (0.85-1.01) 0.081	1.1 (0.96-1.25) 0.068
Triglycerides (mg/dL)	0.972 (0.88-1.06) 0.036	1.03 (0.99-1.00) 0.029	**1.82 (1.59-2.06) 0.043**
Hypertension (mmHg)	0.84 (0.39- 1.83) 0.675	1.25 (0.51-3.27) 0.584	0.596 (0.220-1.16) 0.309
Urea:Creatinine Ratio	0.98 (0.891.07) 0.06	0.933 (0.85-1.018) 0.019	1.007 (0.96-1.054) 0.07

Conclusions: The minor C allele of rs662799 variant lacked direct association with DN in Pakistani subjects. Though in heterozygous status, TC genotype, it seemed to show a protective effect from disease. However the C allele seemed to increase the risk of triglyceridemia in an additive manner. Our results are in accordance with previous studies on other world populations.

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