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ENPP1 K121Q Functional Variant Enhances Susceptibility to Insulin Resistance and Dyslipidemia with Metabolic Syndrome in Asian Indians

Gurjit K. Bhatti[a] Sumanpreet Kaur[b] Rajesh Vijayvergiya[c] Sanjay K. Bhadada[d] Sarabjit S. Mastana[e] Bhupinder Singh[a, f] Jasvinder S. Bhatti[g]

[a]UGC Centre of Excellence in Applications of Nanoapplications, Panjab University, Chandigarh, India; [b]Department of Microbial Biotechnology, Panjab University, Chandigarh, India; [c]Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [d]Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [e]Human Genomics Laboratory, Centre for Global Health and Human Development, School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK; [f]University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India; [g]Department of Biotechnology, Sri Guru Gobind Singh College, Chandigarh, Chandigarh, India

Keywords

ENPP1 gene polymorphism · Metabolic syndrome · Obesity · Dyslipidemia · Asian Indians

Abstract

Background: Ectonucleotide pyrophosphatase/phosphodiesterase1 (ENPP1/PC-1) is a key modulator of the insulin signaling pathway, and its common variant, K121Q, increases the susceptibility to diabetes and cardiovascular diseases. ***Objectives:*** The main objective of the present study was to investigate the association of ENPP1 K121Q polymorphism with the pathophysiology of metabolic syndrome (MetS) in a north Indian population. ***Methods:*** A total of 567 participants (303 MetS subjects and 264 healthy controls) were examined for ENPP1 genotypes and various clinical parameters, including body mass index (BMI), waist circumference (WC), systolic and diastolic blood pressures (SBP/DBP), fasting blood glucose (FBG), cholesterol, triglycerides (TG), high-density lipoprotein, and insulin. Genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Statistical analysis of the data was done using SPSS. ***Results:*** Significant increases in BMI, WC, SBP, DBP, FBG, TG, low-density lipoprotein, insulin, and Homeostasis Model Assessment of insulin resistance (HOMA-IR) and of beta-cell function (HOMA-BF) were observed in MetS patients compared to healthy controls. Logistic regression analysis of data demonstrated a nonsignificant association of QQ and KQ+QQ genotypes with increased risk of MetS (OR [95% CI], 1.583 [0.455–5.507], $p = 0.470$ for QQ genotypes and 1.097 [0.784–1.540], $p = 0.587$ for KQ+QQ genotypes). Moreover, MetS subjects carrying Q alleles had significantly higher levels of TG, insulin, body fat percentage, and insulin resistance as evident by higher values of HOMA-IR. ***Conclusions:*** We conclude that ENPP1 K121Q functional variant enhances susceptibility to insulin resistance and dyslipidemia in MetS subjects of an Asian Indian population.

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E-Mail karger@karger.com
www.karger.com/ijd

Dr. Jasvinder S. Bhatti
Department of Biotechnology
Sri Guru Gobind Singh College
Chandigarh 160019 (India)
E-Mail jasvinderbhatti@yahoo.com

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities comprised of abdominal obesity, hyperinsulinemia, hypertension, and dyslipidemia. India is witnessing a depressing situation due to the escalating incidence and prevalence of MetS in rural and urban populations [1–3]. Earlier data demonstrated that about one-third of the urban population in large cities in India had MetS [4]. The increase in the prevalence of MetS leads to increased morbidity and mortality due to type 2 diabetes mellitus and cardiovascular disease in Asians [5–7]. It has been reported that the prevalence of MetS is 31.4% in an Indian population, and females (48.2%) are more affected than their male counterparts (16.3%) [3, 8]. The origins of MetS are complex and thought to involve metabolic, hormonal, genetic, and lifestyle interactions. Familial segregation analysis, twin studies, and heredity studies clearly demonstrated the genetic basis of MetS [9]. Several candidate genes for defects in insulin signaling pathways have been suggested; however, only a few studies have reported positive associations between polymorphisms of genes in the insulin signaling pathway and insulin resistance [10].

Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1), also known as plasma cell membrane glycoprotein 1 (PC-1), is a membrane glycoprotein that downregulates insulin signaling by interacting with the α-subunit of the insulin receptor [11]. A common missense single nucleotide polymorphism, K121Q (rs1044498) in exon 4 of the ENPP1 gene, has a glutamine substitution for lysine at codon 121 and was found to be associated with insulin resistance [12]. No study has been reported in north Indians, except our previous study [13], so we planned to investigate the possible association of the ENPP1 K121Q polymorphism with the risk of MetS in a north Indian population.

Material and Methods

Human Subjects

We included 567 participants (303 MetS subjects and 264 healthy controls) who were the participants of our ongoing study [14]. In brief, the North Indian Diabetes and Cardiovascular Disease Research (NIDCVD) study was commenced in 2011 with the aim of investigating the interplay of genetic and environmental factors associated with diabetes and cardiovascular diseases in an Indian population. Informed written consent was obtained from all participants. All protocols were approved by the Institutional Ethics Committees of Postgraduate Institute of Medical Education and Research, Chandigarh, India. MetS was defined according to the NCEP-ATP III guidelines with an anthropometric modification of the waist circumference value that is specifically applicable to South Asians [15]. An individual was considered to have MetS when 3 or more of the following criteria were satisfied: (1) central obesity (waist circumference ≥90 cm in men and ≥80 cm in women); (2) elevated blood pressure: systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or known treatment for hypertension; (3) elevated triglycerides (TG): fasting plasma TG ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated TG; (4) reduced high-density lipoprotein cholesterol (HDL-C): fasting HDL-C <40 mg/dL in men and <50 mg/dL in women; and (5) hyperglycemia: elevated fasting glucose >110 mg/dL or previously diagnosed type 2 diabetes. All patients previously diagnosed with MetS and receiving medications for hypertension, diabetes, or dyslipidemia were included in the study and were evaluated for these risk factors.

Anthropometric and Clinical Characteristics

All the anthropometric measurements were performed using standard procedures. Waist and hip circumference were measured with a nonstretchable metal tape. Height was measured with a stature meter and weight with a portable balance beam scale. Blood pressure was measured by an Omron blood pressure machine in sitting position from the left arm resting on the table, with legs uncrossed and feet flat. The quantitative measurements, such as total lipid profile (total cholesterol [TC], TG, HDL, insulin, and creatinine), were recorded from the patients' medical records if done within a maximum of 15 days before participation. Otherwise, these estimations were done in the lab using standard kits (Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald formula, i.e., LDL-C = TC – [HDL-C – (TG in mg/dL/5)]. Fasting and random blood glucose levels were measured using a portable glucometer (Abbott Optium Xceed, USA). All quantitative estimations were done by following the manufacturer's instructions using a biochemistry autoanalyzer.

Derived Measures

Body mass index (BMI) was calculated using the Quetelet equation, i.e., BMI = weight in kilograms/height in meters squared. Waist to hip ratio (WHR) was calculated as the ratio of abdomen to hip circumferences. Anthropometric measurements used for the establishment of abdominal obesity were according to the cutoff values for Asian Indians. Body fat percentage (BF%) was calculated according to the method of Lean et al. [16] using the following formulae: BF% for men = [(0.567 × waist circumference in cm) + (0.101 × age in years)] – 31.8; and BF% for women = [(0.438 × waist circumference in cm) + (0.221 × age in years)] – 9.4. Homeostasis Model Assessment (HOMA) indices, such as insulin resistance (HOMA-IR) and beta-cell function (HOMA-BF), were calculated using the following formulae: HOMA-IR = [fasting insulin (μU/mL) × fasting blood glucose (mmol/L)]/22.5; and HOMA-BF = [20 × fasting insulin (μU/mL)]/fasting blood glucose (mmol/L) [17]. Abdominal obesity was defined according to the cutoffs proposed for South Asian Indians [18], i.e., WHR >0.89 for men and WHR >0.81 for women. BMI <23 has been proposed as low risk, BMI 23–27.5 as increased risk, and BMI ≥27.5 as high risk for developing weight-related diseases in Asian populations.

Amplification of ENPP1 K121Q Polymorphism

Genomic DNA was extracted from the peripheral blood using the phenol/chloroform method. The K121Q polymorphism of ENPP1 polymorphism was detected by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) meth-

Table 1. Anthropometric and clinical measurements in the MetS and control subjects stratified by sex and disease status

Characteristics	Male subjects				Female subjects				Total subjects			
	n	mean	SD	*p* value	*n*	mean	SD	*p* value	*n*	mean	SD	*p* value
Age, years												
Control	113	57.8	14.7	0.204	151	52.4	13.6	0.000	264	54.7	14.3	0.000
MetS	156	59.7	10.2		147	58.3	10.6		303	59.0	10.4	
BMI												
Control	113	26.1	4.3	0.015	151	26.9	5.1	0.000	264	26.6	4.8	0.000
MetS	156	27.4	3.8		147	29.8	4.9		303	28.6	4.5	
WC, inch												
Control	113	36.1	4.4	0.000	151	33.7	4.1	0.000	264	34.7	4.3	0.000
MetS	156	38.6	3.5		147	37.9	4.3		303	38.2	3.9	
HC, inch												
Control	113	37.1	3.2	0.000	151	37.6	3.9	0.000	264	37.4	3.6	0.000
MetS	156	38.6	3.0		147	40.1	4.0		303	39.3	3.6	
WHR												
Control	113	0.97	0.07	0.000	151	0.9	0.1	0.000	264	0.9	0.1	0.000
MetS	156	1.00	0.06		147	0.9	0.1		303	1.0	0.1	
Systolic BP, mm Hg												
Control	113	141	25	0.003	151	134	26	0.000	264	137	26	0.000
MetS	156	149	21		147	151	24		303	150	23	
Diastolic BP, mm Hg												
Control	113	83	13	0.030	151	81	13	0.000	264	82	13	0.000
MetS	156	86	12		147	87	13		303	87	12	

All *p* values <0.05 (two-tailed) were considered significantly different. MetS, metabolic syndrome; SD, standard deviation; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio; BP, blood pressure.

od. The primer sequences were: F 5'GCA ATT CTG TGT TCA CTT TGG A3' and R 5'GAG CAC CTG ACC TTG ACA CA3'. The PCR was performed in a final volume of 25 µL, containing 20 ng of genomic DNA, 1.5 mmol/L $MgCl_2$, 0.2 mmol/L of each deoxynucleotide (Eppendorf, Germany), 0.5 pmol of each primer, and 1 unit of Taq DNA polymerase (New England Biolabs, USA). The initial denaturing was set up at 94 °C for 5 min followed by 30 cycles of denaturation at 94 °C for 50 s, annealing at 55 °C for 40 s, and extension at 72 °C for 40 s, and the final extension was at 72 °C for 5 min. The amplified PCR product (208 bp) was digested with Ava II (New England Biolabs) at 37 °C for 15 h with 1× NEB buffer 4 in a final volume of 15 µL; the reaction was stopped by heat inactivation for 20 min at 65 °C. Results were then analyzed on 2% agarose gel.

Statistical Analysis

Results were expressed as means ± standard deviations. χ^2 analysis was used to test the significance of differences in frequencies. Group comparisons were done using unpaired *t* tests. All *p* values <0.05 (two-tailed) were considered as significant. Logistic regression analyses were performed to correlate various clinical parameters with disease and to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for each risk factor. Statistical analysis was performed using SPSS for Windows, version 20.

Results

Baseline Characteristics of the Study Subjects

In the present study, we assessed the interplay of K121Q polymorphism in the ENPP1 gene and risk of MetS in 567 participants (303 MetS subjects and 264 healthy controls). The baseline characteristics of the study participants are summarized in Table 1. MetS patients demonstrated a significantly higher mean age than the control subjects (59.0 vs. 54.7 years, $p = <0.001$). MetS patients had a pronounced abdominal adiposity reflected by their significantly higher waist circumference (38.2 ± 43.9 inches in patients vs. 34.7 ± 4.3 inches in controls, $p = <0.001$) and WHR (1.0 ± 0.1 in patients vs. 0.93 ± 0.06 in controls, $p = 0.000$). Also, significantly higher values of BMI and elevated blood pressure were observed in MetS patients compared to control subjects ($p < 0.001$). Following stratification of the data based on the new BMI cutoffs by the WHO Expert Consultation (2004), we observed

Table 2. Biochemical parameters in the MetS and control subjects stratified by sex and disease status

Clinical parameters	Male			Female			Total subjects		
	mean	SD	*p* value	mean	SD	*p* value	mean	SD	*p* value
Glucose, mg/dL									
Control	96.4	7.2	0.000	96.6	8.6	0.000	96.0	7.5	0.000
MetS	164.3	66.5		165.4	66.7		164.8	66.5	
TC, mg/dL									
Control	150.4	31.1	0.967	158.8	29.7	0.023	154.5	30.4	0.135
MetS	183.7	50.7		192.9	47.5		188.0	49.3	
TG, mg/dL									
Control	174.2	81.3	0.415	145.5	80.8	0.002	157.7	82.0	0.003
MetS	184.6	87.8		183.4	92.9		184.0	90.1	
HDL-C, mg/dL									
Control	42.5	9.9	0.001	46.2	11.4	0.000	44.6	10.9	0.000
MetS	36.9	11.6		40.3	11.6		38.5	11.7	
LDL-C, mg/dL									
Control	106.1	53.7	0.613	103.5	34.6	0.024	104.6	43.6	0.074
MetS	109.8	48.0		115.9	42.5		112.7	45.5	
VLDL-C, mg/dL									
Control	34.8	16.3	0.415	29.1	16.2	0.002	31.5	16.4	0.003
MetS	36.9	17.6		36.7	18.6		36.8	18.0	
Creatinine, mg/dL									
Control	0.95	0.43	0.789	0.78	0.22	0.953	0.85	0.33	0.700
MetS	0.94	0.27		0.79	0.32		0.87	0.30	
Insulin, IU/mL									
Control	8.3	4.3	0.001	8.4	4.6	0.012	8.3	4.5	0.000
MetS	11.1	6.1		10.5	6.7		10.8	6.4	
Body fat, %									
Control	25.6	6.3	0.000	39.2	5.8	0.000	33.4	9.1	0.000
MetS	29.3	4.9		45.3	5.1		37.1	9.4	
HOMA-IR									
Control	2.15	1.16	0.000	2.01	1.11	0.000	2.07	1.13	0.000
MetS	4.27	2.84		4.09	2.83		4.19	2.83	
HOMA-BF									
Control	95.6	54.9	0.000	92.1	50.3	0.000	93.5	52.0	0.000
MetS	61.3	56.0		56.4	50.0		59.0	53.3	

p values <0.05 (two-tailed) were considered significantly different between MetS and controls. MetS, metabolic syndrome; SD, standard deviation; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of insulin resistance; HOMA-BF, Homeostasis Model Assessment of beta-cell function.

pronounced central obesity in both patients and controls, even at the lowest BMI values (<23).

Table 2 shows the clinical characteristics of MetS patients and healthy subjects stratified by sex and disease status. MetS subjects exhibited significantly higher values of fasting glucose (164.8 ± 66.5 vs. 96 ± 7.5 mg/dL, $p < 0.001$); TG (184 ± 90.1 vs. 157.7 ± 82.0 mg/dL, $p < 0.001$); glycosylated hemoglobin (8.2 ± 2.4 vs. 6.8 ± 2.0%, $p < 0.001$); and insulin (10.8 ± 6.4 vs. 8.3 ± 4.5 IU/mL, $p < 0.001$) as well as reduced HDL-C (38.5 ± 11.7 vs. 44.6 ± 10.9 mg/dL, $p < 0.001$) compared to control subjects. MetS patients demonstrated insulin resistance and beta-

Table 3. Distribution of genotypes and allelic frequencies of ENPP1 K121Q variant in MetS and control subjects

	Controls, *n* (%)	MetS subjects, *n* (%)	Test of association	
			OR (95% CI)	*p* value
Genotypes				
KK	161 (61.0)	178 (58.7)	reference	
KQ	99 (37.5)	118 (38.9)	1.078 (0.766–1.517)	0.666
QQ	4 (1.5)	7 (2.3)	1.583 (0.455–5.507)	0.470
KQ+QQ	103 (39.0)	125 (41.3)	1.097 (0.784–1.540)	0.587
Total genotypes	264	303		
Allele frequencies				
K	421 (0.80)	474 (0.78)	reference	
Q	107 (0.20)	132 (0.22)	1.072 (0.801–1.435)	0.639
Total alleles	528	606		

MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval.

cell dysfunction evidenced by increased values of HOMA-IR and decreased values of HOMA-BF, respectively, in both sexes compared to control subjects. Also, significantly high BF% was observed in MetS patients compared to healthy control subjects ($p < 0.001$). Nevertheless, no significant differences were observed in TC, LDL-C, and creatinine levels of MetS patients compared to control subjects (Table 2).

K121Q Polymorphism in ENPP1 Gene and Risk of MetS

The distribution of genotypes and allele frequencies of the K121Q polymorphism of the ENPP1 gene are given in Table 3. The distribution of KK genotype was slightly higher in control subjects than in MetS patients (61 vs. 58.7%). Subjects with MetS were found to have a slightly higher frequency of KQ and QQ genotypes than control subjects. Very few subjects with QQ genotypes were observed, so we also merged KQ and QQ genotypes to test for an association of the K121Q polymorphism in ENPP1 gene with the risk of MetS. The frequency of the K allele was similar in MetS cases and control subjects ($p = 0.639$).

Logistic regression analysis of data demonstrated a nonsignificant association of QQ and KQ+QQ genotypes with increased risk of MetS (OR [95% CI], 1.583 [0.455–5.507], $p = 0.470$ for QQ genotypes and 1.097 [0.784–1.540], $p = 0.587$ for KQ+QQ genotypes, respectively). In order to evaluate the correlation of the K121Q polymorphism of the ENPP1 gene with metabolic traits, various clinical parameters were analyzed in all participants with KK and KQ/QQ genotypes (Table 4). The results showed that MetS subjects carrying KQ+QQ genotypes had significantly higher levels of TG (174 vs. 199 mg/dL, $p = 0.032$) and VLDL-C (34.9 vs. 39.8 mg/dL, $p = 0.032$) than those carrying KK genotypes. We further evaluated the distribution of the K121Q polymorphism in MetS patients and healthy controls. MetS subjects carrying QQ genotypes showed significantly higher values of HOMA-IR (13.5 ± 1.75) compared to those carrying KK (4.0 ± 2.23) and KQ genotypes (3.7 ± 2.4). Moreover, MetS subjects carrying Q alleles had significantly higher levels of TG, insulin, and BF% than healthy controls. Nevertheless, no significant correlations were observed between the genotypes of the ENPP1 K121Q variant and other metabolic traits in MetS patients or control subjects (Table 4).

Discussion

The incidence and prevalence of MetS is rising globally. The situation of MetS in India has reached an epidemic scale. The findings of previous studies provide evidence for the escalation of MetS and its determinants [5, 19–21]. It has been reported that ENPP1 gene modulates insulin signaling by inhibiting the insulin receptor's tyrosine kinase activity and confers insulin resistance [22]. Further, this effect is modified by the K121Q polymorphism of ENPP1 gene [12]. The consistency of the prediction of the effect of the ENPP1 K121Q allele on type 2 diabetes supports the view that the ENPP1 K121Q allele is the functional variant that affects the phenotype per se [11, 23]. During the last

Table 4. Correlation of ENPP1 K121Q genotypes with measures of quantitative traits in MetS and control subjects

Characteristics/ genotypes	Control subjects			MetS subjects		
	mean	SD	*p* value	mean	SD	*p* value
Age, years						
KK	55.3	14.1	0.405	58.5	10.1	0.314
KQ+QQ	53.8	14.6		59.7	10.8	
BMI						
KK	26.6	5.2	0.924	28.8	4.7	0.239
KQ+QQ	26.6	4.1		28.2	4.3	
WC, inch						
KK	34.6	4.4	0.569	38.4	3.8	0.300
KQ+QQ	34.9	4.3		38.0	4.1	
HC, inch						
KK	37.47	3.67	0.753	39.53	3.59	0.255
KQ+QQ	37.33	3.51		39.04	3.70	
WHR						
KK	0.92	0.08	0.218	0.97	0.07	0.937
KQ+QQ	0.94	0.08		0.97	0.06	
Systolic BP, mm Hg						
KK	139.51	26.29	0.052	149.15	21.65	0.432
KQ+QQ	133.20	24.50		151.22	23.98	
Diastolic BP, mm Hg						
KK	83.17	13.49	0.021	86.96	12.28	0.576
KQ+QQ	79.44	11.39		86.15	12.27	
Glucose, mg/dL						
KK	96.1	7.8	0.699	166.1	67.6	0.682
KQ+QQ	95.7	7.0		163.0	65.0	
TC, mg/dL						
KK	182.8	49.7	0.504	185.2	51.0	0.275
KQ+QQ	178.0	37.6		192.1	46.5	

Characteristics/ genotypes	Control subjects			MetS subjects		
	mean	SD	*p* value	mean	SD	*p* value
TG, mg/dL						
KK	153.1	82.5	0.424	174.3	83.4	0.032
KQ+QQ	163.6	81.7		199.0	97.9	
HDL-C, mg/dL						
KK	46.9	10.9	0.003	38.0	11.8	0.413
KQ+QQ	41.7	10.2		39.2	11.6	
LDL-C, mg/dL						
KK	105.3	48.0	0.807	112.4	46.6	0.900
KQ+QQ	103.6	37.4		113.1	44.1	
VLDL-C, mg/dL						
KK	30.6	16.5	0.424	34.9	16.7	0.032
KQ+QQ	32.7	16.3		39.8	19.6	
Creatinine, mg/dL						
KK	0.87	0.39	0.580	0.88	0.29	0.478
KQ+QQ	0.84	0.25		0.85	0.32	
Insulin, IU/mL						
KK	8.5	4.7	0.680	9.50	6.5	0.008
KQ+QQ	8.2	4.2		11.6	6.0	
Body fat, %						
KK	33.8	8.9	0.425	36.2	8.9	0.042
KQ+QQ	32.8	9.4		39.3	10.0	
HOMA-IR						
KK	2.10	1.19	0.746	2.93	2.98	0.020
KQ+QQ	2.03	1.04		3.65	2.50	
HOMA-BF						
KK	93.6	51.4	0.994	64.0	57.5	0.075
KQ+QQ	93.5	53.4		51.3	45.1	

p values <0.05 (two-tailed) were considered significantly different between genotypes. MetS, metabolic syndrome; SD, standard deviation; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio; BP, blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of insulin resistance; HOMA-BF, Homeostasis Model Assessment of beta-cell function.

decade, genetic association studies have established a positive association between ENPP1 K121Q polymorphism and the pathophysiology of insulin resistance or type 2 diabetes [24–30], obesity [31, 32], and other MetS [30, 33–36]. However, studies of the clinical impact of the K121Q polymorphism have generated conflicting results.

The present study did not predict the association of the ENPP1 K121Q polymorphism with MetS and related quantitative metabolic traits in this population; however, the sample had sufficient power for detecting the association at a moderate level. Among MetS individuals carrying the KQ/QQ genotype, higher values of TG and insulin resistance reflected by HOMA-IR indicated insulin resistance in MetS patients. Recently, a study has demonstrated that the ENPP1 gene polymorphism is associated with hypertriglyceridemia and may contribute to insulin resistance or MetS [37]. Our results are similar to those of a vast majority of studies carried out in different populations. No evidence for an association of the ENPP1 K121Q variant with insulin resistance or type 2 diabetes was reported in Japanese [38], Spanish [39], Danish Caucasian [40], North Indian [13], UK Caucasian [41], and Chinese [42] populations. Besides, a great difference in allele frequencies was observed between the different populations [26, 36, 43]. It is possible that the susceptibility induced by the ENPP1 K121Q gene polymorphism is modulated by

interactions with other ethnicity-specific genetic or environmental factors. Previous studies in Indians and other ethnic groups demonstrated that those carrying the ENPP1 K121Q variant have an increased risk of developing type 2 diabetes and cardiovascular diseases [25, 28, 44, 45]. The same genetic determinants might have a different contribution to the etiology of a complex disease when interacting with different environmental factors. ENPP1 K121Q may contribute to the determination of an ethnic susceptibility to insulin resistance and type 2 diabetes. However, the present data demonstrated the association of the ENPP1 K121Q polymorphism with insulin resistance measured by HOMA-IR, and our results are in line with various studies carried out in other parts of the world [12, 22, 24, 31]. We did not find any association with other metabolic quantitative traits, such as BMI, WHR and TC, LDL-C, and insulin levels. However, the K121Q polymorphism may be associated with insulin resistance and dyslipidemia reflected by low HDL and hypertriglyceridemia in MetS subjects. The reason for the apparent discrepancies between studies, including ours, which have evaluated the pathogenic impact of the K121Q variant, is far from obvious. It is possible that the susceptibility induced by the polymorphism is modulated by interactions with other ethnicity-specific genetic or environmental factors and that the phenotypic expression of the variant will, therefore, be different in various ethnic populations. In this regard, it is emphasized that the frequency of the K121Q polymorphism varies considerably between different ethnic groups. Further, large studies are necessary to ascertain the validity of the described genotype-phenotype relationship in an Asian Indian population. In conclusion, our data suggest that the ENPP1 K121Q polymorphism may be associated with insulin resistance and dyslipidemia in MetS subjects of a north Indian population.

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Statement of Ethics

The study was ethically cleared by the Institutional Ethics Committee of Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.K.B.: planning, data collection, and manuscript writing. S.K.: patient recruitment and data collection. S.K.B.: patient recruitment and data collection. R.V.: patient recruitment and data collection. S.S.M.: performed statistical analysis of the data. B.S.: conceived and designed the data analysis. J.S.B.: conceiving, planning, and implication of the project; data collection, manuscript writing, and submission.

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