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ORIGINAL ARTICLE

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The K121Q polymorphism in the plasma cell membrane glycoprotein 1 gene predisposes to early myocardial infarction

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Abstract Elevated plasma cell membrane glycoprotein 1 (PC-1) expression and the frequent PC-1 K121Q polymorphism have recently been associated with insulin resistance. Since insulin resistance represents an important risk factor for atherosclerotic vascular disease and myocardial infarction, we investigated the involvement of the PC-1 K121Q polymorphism in the development of myocardial infarction. We analyzed two independent series of cardiovascular patients at a defined end-point of atherosclerotic vascular disease (those having suffered myocardial infarction) for the PC-1 K121Q mutation by a newly developed mutagenic separated PCR assay. In both patient groups the presence of the Q allele was significantly associated with younger age at the time of first myocardial infarction, suggesting a more rapid progression of endothelial dysfunction. In a multivariate analysis carriers of the 121Q allele from Vienna and from Central Germany exhibited a 2.6- and a 4.2-increased odds, respectively, for suffering myocardial infarction within the first tertile of age (<51 and <48 years, respectively). Our data indicate that the PC-1 121Q allele might predispose independently of other well established risk factors for early myocardial infarction. Testing for the PC-1 K121Q polymorphism might be valuable in patients with a family history of atherosclerotic vascular disease and myocardial infarction.

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Abbreviations *BMI:* Body mass index · *DM:* Diabetes mellitus · *IR:* Insulin receptor · *MI:* Myocardial infarction · *PC-1:* Plasma cell membrane glycoprotein 1 · *PCR:* Polymerase chain reaction assay

Table 1 Baseline characteristics of MI patients. Univariate *P* values using the third tertile as a reference were calculated and are given below (*parentheses* percentages; Viennese: *first tertile* ≤51 years, *second tertile* 52–59 years, *third tertile* ≥60 years; Central German: *first tertile* ≤47 years, *second tertile* 47–56 years, *third tertile* ≥56 years)

	Viennese patients					Central German patients				
	First tertile (*n*=79)	*P*: first vs. third tertile	Second tertile (*n*=77)	*P*: second vs. third tertile	Third tertile (*n*=78)	First tertile (*n*=70)	*P*: first vs. third tertile	Second tertile (*n*=71)	*P*: second vs. third tertile	Third tertile (*n*=70)
Mean age at time of first MI (years)	43.7±0.6	–	55.0±0.3	–	69.5±0.7	41.5±0.5	–	51.4±0.3	–	64.6±0.8
Male/female	71/8	<0.001	65/12	<0.001	33/45	62/8	<0.001	59/12	0.001	40/30
Smoking	56 (70.9)	<0.001	35 (45.5)	0.002	17 (21.8)	63 (90.0)	0.005	54 (76.1)	0.532	50 (71.4)
Hypertension	51 (64.6)	0.7	61 (79.2)	0.1	53 (67.9)	34 (48.6)	0.089	43 (60.6)	0.779	44 (62.9)
Type II DM	26 (32.9)	0.1	31 (40.3)	0.6	35 (44.9)	13 (18.6)	0.014	18 (25.4)	0.131	26 (37.1)
Hypercholesterolemia	69 (87.3)	0.002	60 (77.9)	0.1	52 (66.7)	34 (48.6)	1.000	42 (59.2)	0.207	34 (48.6)
Hypertriglyceridemia	41 (51.9)	0.2	27 (35.1)	0.5	32 (41.0)	32 (45.75)	0.119	28 (39.4)	0.416	23 (32.9)
Mean BMI (±SEM)	27.8±0.5	0.2	28.2±0.5	0.2	27.0±0.5	26.7±0.5	0.782	27.6±0.4	0.211	26.9±0.5
PC-1 K121Q genotype		0.04		0.03			0.003		0.168	
PC-1 K wild type	55 (69.6)		53 (68.8)		65 (83.3)	42 (60.0)		52 (73.2)		58 (82.9)
PC-1 Q carriers	24 (30.4)		24 (31.2)		13 (16.7)	28 (40.0)		19 (26.8)		12 (17.1)

Introduction

Plasma cell membrane glycoprotein 1 (PC-1, pyrophosphatase 1/alkaline phosphodiesterase 1) is a homodimeric 230- to 260-kDa class II transmembrane protein which is expressed on plasma cells, placenta, distal convoluted tubule of the kidney, ducts of the salivary gland, chondrocytes, osteoblasts, hepatocytes, epididymis, proximal part of the vas deferens, dermal fibroblasts, skeletal muscle, and adipose tissue (reviewed in [1, 2]). It is located both on the plasma membrane and the endoplasmic reticulum and consists of a small N-terminal cytoplasmatic domain and a larger C-terminal extracellular domain, which contains the phosphodiesterase activity. PC-1 is a member of the ectophosphodiesterase family including PD-1α (autotaxin) and PD-1β (B10). The extracellular domain cleaves sugar phosphate, phosphosulfate, pyrophosphate, and phosphodiesterase linkages and thus hydrolyzes ATP (reviewed in [1, 2]). The physiological role of PC-1 is unknown, but it may be important in bone and cartilage metabolism (reviewed in [2]) and lymphocyte function (reviewed in [2]).

PC-1 content is increased in fibroblasts, muscle and adipose tissue from insulin resistant subjects, and its elevation is correlated with in vivo insulin resistance even in the absence of type II diabetes mellitus (DM) or obesity (reviewed in [1, 2]). Although the mechanism is not clear yet, it has been suggested that PC-1 inhibits insulin receptor (IR) signaling via direct interaction with a specific region in the IR α-subunit thereby preventing the insulin-induced conformational change of the α-subunit and the subsequent activation of the β-chain tyrosine kinase [3]. Thus in PC-1 overexpressing cells IR tyrosine kinase activity and the phosphorylation of IR substrate 1, the major substrate for IR, are decreased [4, 5]. Recently, a polymorphism (K121Q) in the exon 4 of the PC-1 gene has been reported to be strongly associated with IR dysfunction and insulin resistance [6, 7] indicating that alterations in either PC-1 expression or structure may disturb the balance between IR kinase activation and its regulatory negative feedback mechanisms (reviewed in [1, 2, 7]).

Since increased PC-1 expression and the presence of the PC-1 121Q allele are associated with insulin resistance and no data are available on a possible association of the PC-1 K121Q polymorphism with the development of atherosclerotic vascular disease and myocardial infarction (MI), we analyzed DNA obtained from 234 patients at a defined endpoint of atherosclerotic vascular disease (Table 1), i.e., patients who had suffered MI, for the presence of the PC-1 121Q allele. We confirmed the findings in these patient group in a second, independent series from Central Germany which was kindly provided by Prof. P. Hellstern.

Patients and methods

Subjects

This study was carried out between November 1999 and August 2000 at the General Hospital of Vienna, Austria and included 234 patients (181 men, 53 women) who had suffered MI according to WHO criteria [8] (mean age at time of MI 56.0±0.8 years, range 26–85. The study was approved by the local ethics committee, and all patients gave their written informed consent. A total of 221 patients underwent coronary angiography for the determination of the extent of coronary artery disease. Routine laboratory parameters, hemoglobin A_{1c}, and lipid profiles were analyzed at the time of admission. All patients were questioned for known cardiovascular risk factors including diabetes, smoking (>20 cigarettes for more than 5 years), hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) at repeated measurements or a known history of hypertension and treatment with antihypertensive drugs [9], body mass index (BMI), and family history (Table 1). Hypercholesterolemia was defined as base-

Table 2 Clinical characteristics of the controls without coronary artery disease. Univariate *P* values comparing PC-1 wild type to carriers of the 121Q allele were evaluated using the χ^2 test for dichotomous variables and the Mann-Whitney *U* test for continuous variables (*parentheses* percentages)

	Viennese patients				Central German patients			
	Total (*n*=310)	PC-1 121K wild type (*n*=240)	PC-1Q carriers (*n*=70)	*P*	Total (*n*=299)	PC-1 121 wild type K (*n*=217)	PC-1Q carriers (*n*=82)	*P*
Mean age (years)	57.5±0.88	58.0±0.99	55.6±1.92	0.361	57.6±0.8	57.1±0.9	58.9±1.4	0.474
Male/female	155/155	126/114	29/41	0.103	152/147	104/113	48/34	0.102
Smoking	61 (19.7)	47 (19.6)	14 (20.0)	0.939	144 (48.2)	101 (46.5)	43 (52.4)	0.363
Hypertension	117 (37.7)	85 (35.4)	32 (45.7)	0.118	151 (50.5)	116 (53.5)	35 (42.7)	0.096
Type II DM	38 (12.3)	32 (13.3)	6 (8.6)	0.285	59 (19.7)	42 (19.4)	17 (20.7)	0.790
Hypercholesterolemia	99 (31.9)	73 (30.4)	26 (37.1)	0.288	192 (64.2)	143 (65.9)	49 (59.8)	0.323

line cholesterol levels above 200 mg/dl or serum low-density lipoprotein levels above 130 mg/dl, and hypertriglyceridemia as triglyceride levels above 200 mg/dl after overnight fasting [10]. DM was considered present in patients with a known history of diabetes and in patients with a fasting glucose level higher than 126 mg/dl according to American Diabetes Association criteria [11]. The prevalence of the PC-1 K121Q polymorphism in the Austrian population was evaluated in 310 patients (155 men, 155 women; mean age 57.5±0.9 years, range 17–92 years) for whom the presence of relevant coronary artery disease could be excluded by ergometry and/or thallium persantin scan and coronary angiography where indicated (Table 2).

Atherosclerosis is a continuous process starting before birth [12] and becoming symptomatic at advanced age. We studied whether the PC-1 genotype has an effect on the manifestation of atherosclerosis predisposing to MI. We evaluated the distribution of the PC-1 genotype among patients with MI using the age at first MI as a dependent variable. We, therefore, divided the patients into tertiles according to their age at first MI: before the age of 51 years (*n*=79), between 52 and 59 years of age (*n*=77), and at the age of 60 years or over (*n*=78).

To confirm our findings, we analyzed a series of 211 patients from Central Germany (LURIC study) with a history of MI according to WHO criteria for the presence of the PC-1 121Q allele. The German patients were characterized for established cardiovascular risk factors according to the same criteria as described for the Viennese series (Table 1). In addition, 299 controls of Central German origin without coronary artery disease confirmed by coronary angiography were tested for the PC-1 K121Q polymorphism (Table 2).

PCR analysis of the PC-1 K121Q polymorphism

Blood (4 ml) was drawn during a routine venupuncture after obtaining the patient's informed consent for DNA analyses. DNA was isolated according to standard procedures. To determine the PC-1 A/C single nucleotide polymorphism (K121Q; AF067177 and AF067178), we adapted a mutagenic separated polymerase chain reaction assay (PCR), a single-tube PCR based technique relying on allele specific primers that differ in length by 8–10 bp and resulting in PCR products of different size [13]. Various single-base mismatches in the allele specific primers (indicated below in italic) introduce deliberate differences into the allelic PCR products to minimize crossreactions of the PCR products in subsequent cycles. One or two different PCR products are amplified depending on the genotype. PCR products were generated in 50 µl volumes containing 1.25 U AmpliTaq Gold (Perkin Elmer Cetus, Norwalk, Conn., USA), 1.5 mM $MgCl_2$, 2 µM of each deoxyribonucleoside triphosphate (Amersham Pharmacia Biotech, Uppsala, Sweden), 13 pmol PC-1 121K reverse primer (5′-AGT TGC TGC AGC AGT CGC GCT T-3′, nn 87–108), 7 pmol PC-1 121Q reverse primer (5′- AGA ACT GT*T AA*T GAT GCA GCA GTC G*A*C CTG-3′, nn 87–116), 13 pmol common forward primer (5′-GGA CTT GCA ACA AAT TCA GGT GTG GT-3′, nn 10–35), all synthesized by MWG Biotech (Ebersberg, Germany), and approximately 50 ng DNA. Amplifications were performed in a Perkin Elmer 480 DNA Thermo Cycler (Perkin Elmer Cetus, Emeryville, Calif., USA). A 10-min denaturation period at 95°C was followed by 37 cycles of 95°C for 1 min, 54°C for 2 min, and 72°C for 1 min. A final extension step of 7 min at 72° completed the reaction. For the PC-1 121K allele a PCR product with a length of 99 bp and for the PC-1 121Q allele a product of 107 bp were generated and separated on precast 6% Tris-borate-EDTA polyacrylamide gels (Novex, San Diego, Calif., USA) for 45 min at 160 V. After staining with Sybr Green (Molecular Probes, Eugene, Ore.,USA) for 20 min bands were visualized on an UV transilluminator at 306 nm and photographed.

Statistical analysis

For statistical analyses we used the SPSS 10.0 software package (SPSS, Chicago, Ill., USA). Mean values and standard error of the mean are given. Univariate analysis was performed using a nonparametric Mann-Whitney *U* test, a two-tailed *P* value less than 0.05 was considered statistically significant. Correlation of continuous variables was determined by Spearman's correlation coefficient. Multivariate analysis using a polynominal logistic regression model was applied to assess the independent association of the genotype and patients' age at first MI. The age at first MI was divided into tertiles and entered as the dependent variable into the model. The following variables which are well known risk factors for early MI were included as covariates in the model to adjust for confounding: sex, hypercholesterolemia, hypertriglyceridemia, hypertension, DM, smoking, and BMI. For all variables odds ratios and 95% confidence intervals) were calculated.

Results

Among the 234 persons in the Viennese series who suffered MI 173 (74.9%) exhibited wild-type PC-1 121K, 58 (24.8%) were heterozygous PC-1 K121Q, and 3 (1.3%) were homozygous for PC-1 121Q. Genotype frequencies were similar in diabetics [total 92; 25 (27.2%) heterozygous K121Q, 1 (1.1%) homozygous for 121Q] and patients without a known history of DM [total 142; 33 (23.2%) heterozygous K121Q and 2 (1.4%) homozygous for 121Q]. Genotype frequencies were in Hardy-Weinberg equilibrium in all groups. Since only 3 individuals were carriers of the QQ genotype, they were includ-

Table 3 Mean age at time of first MI. *P* values are calculated univariately using the Mann-Whitney *U* test

Genotype	Viennese patients (*n*=234)			Central German patients (*n*=211)		
	n	Age (years)	*P*	*n*	Age (years)	*P*
PC-1 121K wild type	173	57.0±0.9	0.04	152	53.7±1.2	0.005
PC-1Q carriers	61	53.3±1.4		59	49.5±1.3	

Table 4 Polynomial logistic regression model assessing the independent association of the PC-1 genotype and patient's age at the time of MI; comparisons are of the first and second tertiles vs. the third. Model adjusts for sex, BMI, hypercholesterolemia, hypertriglyceridemia, arterial hypertension, diabetes mellitus, and smoking (Viennese: *first tertile* ≤51 years, *second tertile* 52–59 years, *third tertile* ≥60 years; Central German: *first tertile* ≤47 years, *second tertile* 47–56 years, *third tertile* ≥56 years)

	Viennese patients			Central German Patients		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
First tertile	2.6	1.1–6.5	0.03	4.2	1.6–11.2	0.005
Second tertile	2.5	1.1–5.9	0.03	2.5	1.0–6.5	0.056
Third tertile	1.0	–	–	1.0	–	–

ed in the KQ group (*n*=58), further referred to as Q allele carriers.

No significant association was observed between PC-1 genotype and fasting glucose levels, hemoglobin A_{1c} values, DM, BMI, lipid profiles, or other cardiovascular risk factors. However, in the 234 patients with MI the presence of the Q allele was significantly associated with a younger age at the time of first MI (*P*=0.04). Mean age at time of first MI was 57.0±0.9 years in PC-1 121KK individuals and 53.3±1.4 years in Q allele carriers (Table 3). The distribution of other cardiovascular risk factors did not differ between the groups of patients with either genotype (data not shown). Additionally, multivariate analysis adjusting for sex, DM, hypercholesterolemia, hypertriglyceridemia, BMI, and smoking revealed the PC-1 121Q allele as an independent risk factor (odds ratio 2.6, 95% confidence intervals 1.1–6.5) for suffering the first MI at a younger age (Fig. 1) – in the Viennese series within the first or second tertile of age (<60 years, Table 4).

Similar results were obtained in an independent series of Central German origin (Table 4). Of 70 patients who suffered MI within the third tertile of age (≥56 years) 12 (17.1%) were carriers of the 121Q allele, while 19 of 71 (26.8%) within the second tertile (47–56 years) carried the 121Q allele (*P*=0.17), and 28 of 70 (40%) of the patients within the first tertile (≤47 years) carried the 121Q allele (*P*=0.003, Table 1). Interestingly, in the Central German series the 121Q allele was an independent risk factor for MI only in the first tertile of age. This association remained statistically significant (odds ratio 4.2, 95% confidence intervals 1.6–11.2, *P*=0.005) in a multivariate analysis adjusting for sex, BMI, hypercholesterolemia, hypertriglyceridemia, arterial hypertension, diabetes mellitus, and smoking (Table 4). Within the control groups without coronary artery disease 22.6% (70/310) in the Viennese series and 27.4% (82/299) in the Central German series carried the 121Q allele. No associations were observed

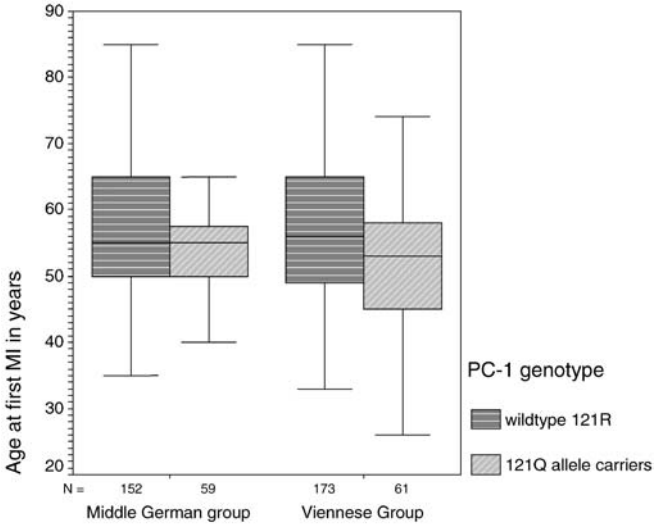

Fig. 1 shows the age distribution in both series depending on the PC-1 genotype. In both series individuals carrying the PC-1 121Q allele suffered their first MI at a significantly younger age. *P*<0.05 in both series

in either series of controls between the PC-1 121Q allele and age (Table 2). Stratifying each series in terms of tertiles according to age, no association between the 121Q frequencies and age was observed (25.7% in the first tertile, 18.6% in the second tertile, and 23.2% in the third tertile in the Viennese series and 24.2%; 30.1%, and 28% in the Central German series).

Regarding limitations of the study, the impact of a single nucleotide polymorphism on a complex disease such as MI, is no doubt affected by such factors as patient selection, ethnic background, and sample size. Our series represents a cross-section of survivors of MI. Patients with MI who died of sudden cardiac death before reaching the hospital could not be included in our study. Therefore our findings can only be applied to survivors of MI.

Discussion

Cardiovascular disease is the major cause of morbidity and mortality in the Western World. Although atherosclerosis is a multifactorial systemic vascular process manifesting primarily as heart attack and stroke and progressing with age, premature atherosclerosis may occur in patients presenting with excess low-density lipoprotein cholesterol, DM, hypertension, and cigarette smoking – the classical risk factors for cardiovascular disease [14]. Additionally, inherited risk factors may contribute to the development of premature atherosclerosis including polymorphisms in coagulation factors and in platelet glycoprotein receptors (reviewed in [15]), the E-selectin gene (L/F554) polymorphism, and the glycoprotein IIb/IIIa variant [16]. Type II DM is commonly associated with cardiovascular risk factors (hypertension, overweight, hyperlipidemia) that occur predominantly as a result of insulin resistance, hyperinsulinemia, and hyperglycemia. Insulin resistance precedes the onset of type II DM for several years, interferes with vascular homeostasis (modulating vascular tone, regulating local cellular growth, extracellular matrix deposition, and hemostatic, inflammatory and reparative responses to local injury), and thus contributes to a proatherogenic environment [17].

Contradictory results have been reported regarding the involvement of PC-1 in insulin resistance, although PC-1 was shown to interact with the IR α-chain and to inhibit IR signaling [6, 18]. Costanzo et al. [7] demonstrated that the PC-1 121Q allele interacts in a tighter/stronger way with the IR than with the PC-1 121K allele, which may represent the mechanism by which the 121Q genotype contributes to the development of insulin resistance. Since our data obtained from two independent series of cardiovascular patients suggest that the common PC-1 K121Q polymorphism predisposes to a rapid progression of atherosclerosis resulting in MI at a younger age, the PC-1 K121Q polymorphism may be considered as a risk factor for early MI. Further studies must consider the genetic risk of MI in a multigenetic approach, in which the PC-1 K121Q polymorphism should be included.

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