

## Brief Genetics Report

# The K121Q Polymorphism of the *ENPP1/PC-1* Gene Is Associated With Insulin Resistance/Atherogenic Phenotypes, Including Earlier Onset of Type 2 Diabetes and Myocardial Infarction

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Insulin resistance (IR) is pathogenic for type 2 diabetes and coronary artery disease (CAD). The K121Q polymorphism of the *ENPP1/PC-1* gene is associated with IR. Our aim was to investigate the role of the 121Q variant on the risk of type 2 diabetes and CAD. Nondiabetic control subjects ( $n = 638$ ), type 2 diabetic patients without CAD ( $n = 535$ ), and type 2 diabetic patients with CAD ( $n = 434$ ) from Italy and the U.S. were studied. The proportion of 121Q carriers progressively increased in the three groups (27.4, 28.8, and 33.2%, respectively; adjusted  $P$  value = 0.027). Among diabetic patients ( $n = 969$ ), 121Q carriers had an increased risk of developing type 2 diabetes before the age of 65 years (adjusted odds ratio [OR] 2.26, 95% CI 1.26–4.03;  $P = 0.006$ ) and having a myocardial infarction (MI) ( $n = 156$ ) by 50 years of age (3.17, 1.46–6.88,  $P = 0.007$ ). The 121Q variant was also associated with an increased risk for CAD (1.47, 1.01–2.18;  $P = 0.049$ ) in diabetic patients who did not smoke ( $n = 546$ ). In conclusion, the *ENPP1/PC-1* 121Q variant is associated with a progressive deterioration of the IR-atherogenic phenotype; among diabetic individuals, it is also associated with earlier onset of type 2 diabetes and MI. *Diabetes* 54:3021–3025, 2005

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CAD, coronary artery disease; FP, fluorescence polarization; IR, insulin resistance; MI, myocardial infarction; OR, odds ratio.

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Although it is well accepted that insulin resistance (IR) is partly under genetic control, the genes that are involved are mostly unknown (1–5). IR is pathogenic for type 2 diabetes (6) and, especially among diabetic patients, for coronary artery disease (CAD) (7). Thus, IR genes are likely to play a modulating role in the development and/or severity of both type 2 diabetes and its cardiovascular complications. The ectoenzyme nucleotide pyrophosphate phosphodiesterase (ENPP1, also known as plasma cell membrane glycoprotein 1, or PC-1) is a class II membrane glycoprotein that adversely influences insulin sensitivity by inhibiting insulin receptor signaling (8–10). A functional missense polymorphism (i.e., K121Q) of the *ENPP1/PC-1* gene has been recently described (11). ENPP1/PC-1 protein binds to the insulin receptor molecule, causing inhibition of the tyrosine kinase domain (9). The 121Q variant binds insulin receptor more strongly than the 121K variant (12). It is therefore a stronger inhibitor of insulin signaling and is associated with IR and related abnormalities in the vast majority of the studied populations (11,13–17). In contrast, conflicting results have been reported about the effect of the *ENPP1/PC-1* 121Q variant on risk for type 2 diabetes (11,13,15,18–20), and no data are available on the role of this variant in modulating the risk and severity of CAD in type 2 diabetic patients. In the present study, we investigated the role of the *ENPP1/PC-1* 121Q variant on the risk of type 2 diabetes and its cardiovascular complications in Caucasians from Italy and the U.S. To this end, we compared the proportion of 121Q carriers in three groups of individuals characterized by a progressive increase of the IR/atherogenic clinical phenotype, from normoglycemia to type 2 diabetes not complicated by CAD and to type 2 diabetes complicated by CAD.

Two populations were investigated in this study, one from Gargano in the central eastern region of Italy and the other from Boston, Massachusetts. Each population included two groups of subjects with type 2 diabetes (with and without clinical evidence of CAD) and a group of nondiabetic control subjects. (The salient clinical features of the three study groups are shown in Table 1.) In the population from Italy, the proportion of subjects carrying

TABLE 1  
Clinical features in nondiabetic control subjects and patients with type 2 diabetes with or without CAD

	Gargano			Boston			All		
	Control subjects	Type 2 diabetic patients without CAD	Type 2 diabetic patients with CAD	Control subjects	Type 2 diabetic patients without CAD	Type 2 diabetic patients with CAD	Control subjects	Type 2 diabetic patients without CAD	Type 2 diabetic patients with CAD
<i>n</i>	352	333	228	286	202	206	638	535	434
Age (years)	45 ± 8	60 ± 8	64 ± 8	62 ± 14	65 ± 6	65 ± 7	53 ± 14	62 ± 8	64 ± 8
Men/women ( <i>n</i> )	125/227	140/193	155/73	150/135	117/85	135/71	276/362	257/278	290/144
BMI (kg/m <sup>2</sup> )	27 ± 4	31 ± 5	30 ± 4	26 ± 5	32 ± 5	32 ± 6	27 ± 5	31 ± 5	31 ± 5
Smoking (%)	—	25	44	—	43	70	—	35	57
Hypertension (%)	—	74	78	—	76	81	—	74	77
A1C (%)	—	8.5 ± 2	8.6 ± 2	—	7.2 ± 1.2	7.2 ± 1.3	—	8.0 ± 2	7.9 ± 2
Diabetes duration (years)	—	11.8 ± 8	14.7 ± 9	—	12.3 ± 6	11.7 ± 8	—	11.9 ± 7	13.2 ± 9

Data are means ± SD unless otherwise indicated.

the *ENPP1/PC-1* 121Q variant (i.e., carrying either the K121Q or the Q121Q genotype, indicated as X121Q) progressively increased from nondiabetic control subjects to type 2 diabetic patients without CAD and to type 2 diabetic patients with CAD (92 of 352 [26.1%] vs. 91 of 333 [27.3%] and 77 of 228 [33.8%], respectively; *P* for trend = 0.026, after adjusting for age, sex, and BMI). A similar trend, although not statistically significant with this sample size (*P* = 0.44), was observed across the three phenotype groups in the population from Boston (83 of 286 [29%] vs. 63 of 202 [31.2%] and 67 of 206 [32.5%], respectively). The association between 121Q and the phenotype was not statistically different between the groups from Italy and Boston (*P* for interaction = 0.55) and, when the two

populations were analyzed together, a significant increase in the prevalence of the 121Q allele was observed across the nondiabetic control subjects (175 of 638 [27.4%]) to type 2 diabetic patients without CAD (154 of 535 [28.8%]) and to type 2 diabetic patients with CAD (144 of 434 [33.2%]; *P* for trend = 0.027, after adjusting for age, sex, BMI, and place of recruitment). As many as 20–25% of nondiabetic control subjects are likely to be insulin resistant (6); if these individuals would have been excluded from the analysis, the difference in the 121Q allele proportion between nondiabetic and diabetic individuals would have been even greater. The described association was observed in individuals with a BMI ≥28 kg/m<sup>2</sup> (121Q frequencies = 26% in nondiabetic control subjects vs. 28.4%

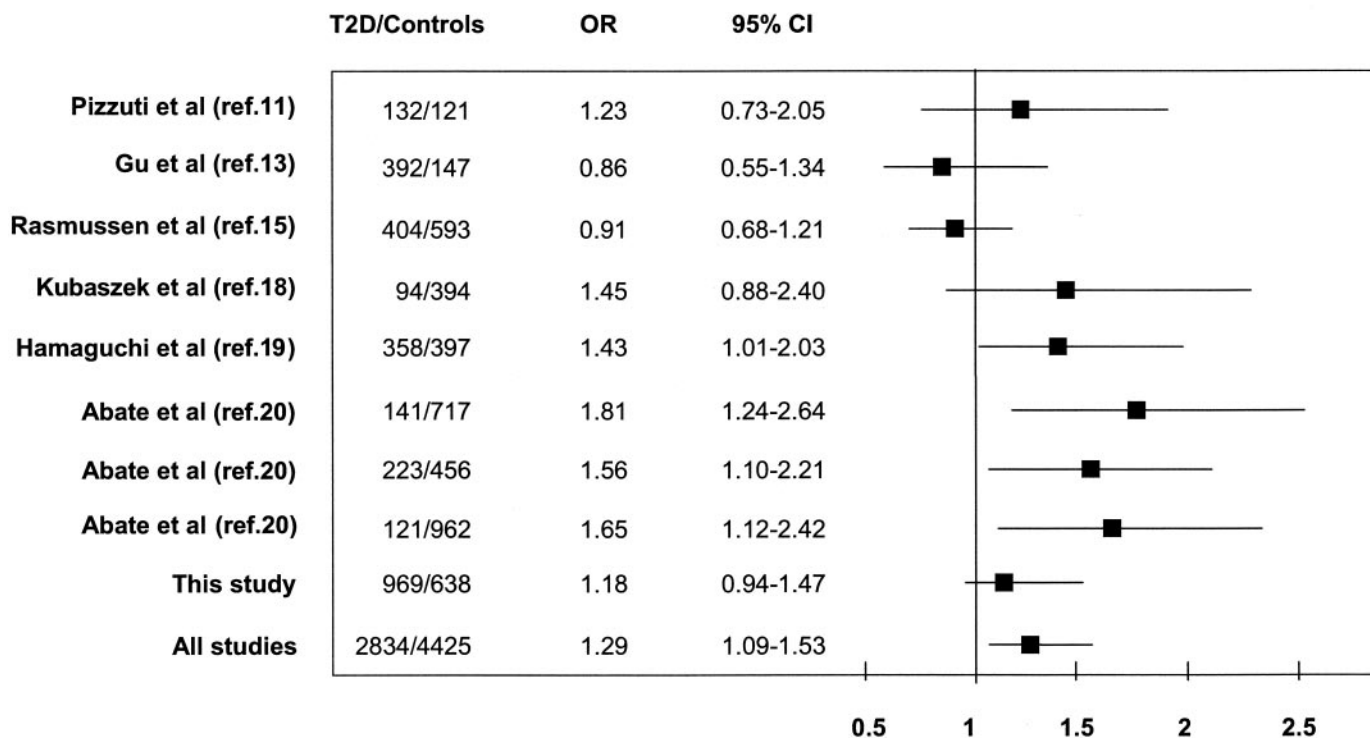


FIG. 1. Meta-analysis of all published case-control studies on the association of the *ENPP1/PC-1* 121Q variant with type 2 diabetes. The reference numbers of reported studies are indicated in parentheses. *P* value of Cochran's *Q* test for heterogeneity = 0.04. T2D/Controls, number of type 2 diabetic patients/number of nondiabetic control subjects.

TABLE 2

Risk of developing type 2 diabetes before the age of 65 years, according to the *ENPP1/PC-1* K121Q genotype

K121Q genotype	Age of onset (years)		OR* (95% CI)	P	OR† (95% CI)	P
	<65 [n (%)]	≥65 [n (%)]				
K121K	580 (68)	95 (82)	1		1	
X121Q	273 (32)	21 (18)	2.16 (1.23–3.80)	0.007	2.26 (1.26–4.03)	0.006

\*Adjusted for sex and place of recruitment; †adjusted for sex, place of recruitment, and BMI.

in type 2 diabetic patients without CAD vs. 35.9% in type 2 diabetic patients with CAD;  $P$  for trend = 0.01), but not among individuals with a BMI <28 kg/m<sup>2</sup> (121Q frequencies = 28.1 vs. 29.8 vs. 26.7%, respectively;  $P$  for trend = 0.82). Such a difference between BMI strata in the 121Q association with IR/atherogenic phenotypes was significant ( $P$  for interaction = 0.042), in agreement with a recent report describing a similar effect in nondiabetic individuals (20).

When all diabetic individuals (i.e., those with and without CAD) were compared with control subjects, the 121Q allele had a tendency to be associated with type 2 diabetes (adjusted odds ratio [OR] 1.21, 95% CI 0.94–1.56). While this effect was not significant with this sample size (adjusted  $P$  = 0.13), its magnitude was not significantly different from the values reported in eight previous studies of the 121Q variant as a risk factor for type 2 diabetes ( $P$  = 0.24, by  $\chi^2$  analysis). When all studies (including the present one) were considered together in a meta-analysis, resulting in a total of 4,425 control subjects and 2,834 type 2 diabetic subjects, the pooled OR was 1.29, with the 95% CI ranging from 1.09 to 1.53 ( $P$  = 0.003) (Fig. 1). This value is in the same range of that reported for well-established genetic determinants of type 2 diabetes (3) and agrees with a model in which type 2 diabetes susceptibility is conferred by several genes, each having a relatively small effect (1). Among all type 2 diabetic patients, those carrying the 121Q variant had an approximate twofold increased risk of developing type 2 diabetes before the age of 65 years (Table 2).

The 121Q allele was not significantly associated with the occurrence of CAD among type 2 diabetic patients (adjusted OR 1.35, 95% CI 0.94–1.95;  $P$  = 0.10). However, the proportion of 121Q carriers was significantly higher in the group with CAD (36%) compared with the group without CAD (28.8%) when the analysis was restricted to nonsmokers ( $n$  = 546, OR 1.52, 95% CI 1.01–2.18;  $P$  = 0.049 after adjusting for age, sex, place of recruitment, BMI, and hypertension). Among type 2 diabetic patients with CAD who had a myocardial infarction (MI) ( $n$  = 156), the age at MI was progressively and significantly ( $P$  = 0.01) reduced from K121K ( $n$  = 106;  $57 \pm 8$  years) to K121Q ( $n$  = 42;  $56 \pm 9$  years) to Q121Q ( $n$  = 8;  $48 \pm 8$  years) genotype carriers, an association that remained significant after adjusting for sex, BMI, smoking, hypertension, and place of recruitment ( $P$  = 0.04). As compared with K121K

subjects, 121Q carriers had a threefold increase in the risk of developing MI by age 50 years rather than at a later age (Table 3). In addition, BMI was inversely related to age at MI in patients carrying the 121Q variant ( $\beta$  = -0.305;  $P$  = 0.03 after adjusting for sex, smoking, hypertension, and place of recruitment) but not in K121K carriers ( $\beta$  = -0.041, adjusted  $P$  value = 0.67), providing further support to the notion that BMI and the 121Q variant interact to produce an IR/atherogenic phenotype (adjusted  $P$  value for BMI/K121Q polymorphism interaction = 0.05). The contribution to early MI risk showed by the *ENPP1/PC-1* 121Q variant in this study is reminiscent of previous data in individuals from the general population (21), thus suggesting that the role of the 121Q variant in accelerating the atherogenic process may be a generalized phenomenon not restricted to the diabetic population.

Given the increased risk of earlier onset type 2 diabetes and MI, 121Q carriers are likely to be affected by increased mortality rate. This is also suggested by the lower proportion of 121Q variant carriers in the last age decade (>70 years old) of the entire cohort of type 2 diabetes (OR 0.66, 95% CI 0.44–0.96;  $P$  = 0.048 after adjusting for sex, smoking, and place of recruitment). Of note, an increased mortality rate of 121Q diabetic carriers, if any, would have weakened the association with diabetes, thus underestimating the real impact of this variant on the risk of type 2 diabetes.

In conclusion, our data indicate that the *ENPP1/PC-1* 121Q variant is associated with a progressive deterioration of the IR/atherogenic clinical phenotype from the absence of type 2 diabetes to type 2 diabetes not complicated by CAD and to type 2 diabetes with CAD. Among diabetic patients, the 121Q variant is associated with an earlier onset of type 2 diabetes and MI. If these associations are confirmed in other populations, the PC-1 K121Q polymorphism may help identify individuals who are prone to develop earlier type 2 diabetes at high risk for coronary disease.

## RESEARCH DESIGN AND METHODS

**Subjects from Italy.** Five hundred sixty-one patients with type 2 diabetes (defined according to the World Health Organization criteria) who resided in the Gargano and the surrounding central eastern region of Italy and attended the Scientific Institute "Casa Sollievo della Sofferenza" in San Giovanni Rotondo were included in the study. Two hundred twenty-eight of them had

TABLE 3

Risk of earlier ( $\leq 50$  years) MI according to the *ENPP1/PC-1* K121Q in patients with type 2 diabetes

K121Q genotype	Age at MI (years)		OR* (95% CI)	P	OR† (95% CI)	P
	$\leq 50$ [n (%)]	>50 [n (%)]				
K121K	23 (51.1)	83 (74.8)	1		1	
X121Q	22 (48.9)	28 (25.2)	3.17 (1.46–6.88)	0.003	2.98 (1.35–6.59)	0.007

\*Adjusted for sex, smoking, and place of recruitment; †adjusted for sex, smoking, place of recruitment, and hypertension.

significant CAD, defined as either a >50% reduction in diameter of at least one major vessel at coronary angiography and/or a previous MI (22). The remaining 333 patients did not have symptoms or resting electrocardiogram (ECG) signs of myocardial ischemia and had a normal exercise treadmill test (ETT) according to a standard Bruce protocol. An additional group of 352 nondiabetic, unrelated Caucasian residents of the same region was included in the study according to the following selection criteria: age in the same range of type 2 diabetic patients (i.e., 35–76 years), fasting plasma glucose <6.1 mmol/l, and on no medication known to affect glucose and lipid metabolism. Salient clinical features of the three study groups are shown in Table 1.

**Subjects from Boston.** Four hundred eight Caucasian type 2 diabetic patients from this location were included in the study. Subjects with significant CAD (stenosis >50% in at least one major coronary artery or their main branches,  $n = 206$ ) were recruited among type 2 diabetic patients who underwent cardiac catheterization at the Beth Israel Deaconess Medical Center (BIDMC). CAD-negative type 2 diabetic patients ( $n = 202$ ) were patients of the Joslin Diabetes Clinic (the Joslin Diabetes Clinic serves as the BIDMC Diabetes Clinic) who were aged 55 years or older, had had type 2 diabetes for  $\geq 5$  years, and had a negative cardiovascular history, a normal resting ECG, and a normal ETT according to a standard Bruce protocol. Nondiabetic control subjects were unrelated nondiabetic spouses of subjects with type 2 diabetes and nondiabetic parents of patients with type 1 diabetes who are enrolled in family studies currently under way at the Joslin Diabetes Clinic. All control subjects had a negative history for type 2 diabetes, were not currently taking any glucose-lowering medications, and had fasting glucose <6.1 mmol/l or an HbA<sub>1c</sub> (A1C) value <6.1%. Clinical features of the three groups studied are shown in Table 1. Genotypes frequencies in each group were in Hardy-Weinberg equilibrium.

**Laboratory methods.** All study subjects were examined between 8:00 and 9:00 A.M. after an overnight fast. A1C was determined by high-pressure liquid chromatography after removal of the labile fraction (HPLC Diamat Analyzer; Bio-Rad, Richmond, CA). The presence of hypertension was considered if systolic blood pressure was >130 mmHg and diastolic blood pressure was >85 mmHg or if patients were on antihypertensive therapy.

The K121Q polymorphism of the *ENPP1/PC-1* gene in individuals from Italy was determined as previously described (11). Exon 4 amplicons were obtained using the following primer pair: 4-forward, 5'-GCAATTCGTGTGTTCACTTTGGA-3'; and 4-reverse, 5'-GAGCACCTGACCTTGACACA-3'. The PCR was carried out in a final volume of 25  $\mu$ l, containing 100 ng genomic DNA, 1.5 mmol/l MgCl<sub>2</sub>, 0.2 mmol/l of each deoxynucleotide triphosphate, 0.5 pmol of each primer, and 0.05 units of *Taq* polymerase (Euroclone). After an initial denaturation of 2 min at 94°C, the samples were subjected to 30 cycles at 94°C for 1 min, 55°C for 40 s, and 72°C for 40 s, with a final extension of 10 min at 72°C. The 208-bp product was restricted with *Ava*II for 2 h at 37°C. The unrestricted 208-bp product represents the K allele, while the Q allele was cut into 53- and 155-bp fragments. The three genotypes were scored after running on a 2.5% agarose gel and staining with ethidium bromide. Individuals from Boston were genotyped by a single base extension (SBE)/fluorescence polarization (FP). DNA fragments containing the K121Q polymorphism were amplified using the same primers and conditions that were used for the Italian population. After removing the excess primers and dNTPs by means of exonuclease and shrimp alkaline phosphatase, the SBE reaction was performed using the AcycloPrime-FP SNP Detection Kit (Perkin Elmer) according to the manufacturer's protocol with the oligonucleotide AACTGTAGTTGATGCAGCAGTCGCCCT as a primer. FP was measured by means of a Wallac VICTOR2 Multilabel Plate Reader (Perkin Elmer).

**Statistical methods.** All statistical analyses, except for the meta-analysis, were performed using the SPSS statistical package (Version 11; Chicago, IL). The association between K121Q genotype and phenotype was evaluated by ordinal logistic regression in the case of the three-level phenotype (nondiabetic subjects vs. type 2 diabetic patients without CAD vs. type 2 diabetic patients with CAD) and logistic regression in the case of binary phenotypes. Differences in the association between recruitment centers or BMI strata were evaluated by adding interaction terms obtained by multiplying the genotype indicator variable (coded as 0;1) by the recruitment location or the BMI indicator variable (also coded as 0;1). Linear regression was used to compare continuous variables (expressed as means  $\pm$  SD) and to test for interaction between genotype and place of recruitment or BMI. A *P* value <0.05 was considered as significant. A random effect meta-analysis following the DerSimonian-Laird approach (23) was performed using a macro-routine written in SAS Language (Release 9.1; SAS, Cary, NC).

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