J Korean Med Sci 2008; 23: 459-64
ISSN 1011-8934
DOI: 10.3346/jkms.2008.23.3.459

The K121Q Polymorphism in *ENPP1* (PC-1) Is Not Associated with Type 2 Diabetes or Obesity in Korean Male Workers

Type 2 diabetes is characterized by insulin resistance, and *ENPP1* plays an important role in insulin resistance. We investigated the association of the *ENPP1* K121Q polymorphism with both diabetes and obesity (body mass index [BMI]) in Korean male workers. The study design was case-control. Subjects were 1,945 male workers (type 2 diabetes, 195; non-diabetes, 1,750) of nuclear power plants who received examinations from March to October in 2004. We collected venous blood samples under fasting (≥8 hr) conditions, calculated BMI by height and weight, and assessed relevant biochemical factors. The results of this study demonstrated that the *ENPP1* 121Q genotype (KQ+QQ types) was not associated with type 2 diabetes (odds ratios [OR], 0.854; 95% confidence interval [CI], 0.571-1.278) or obesity (OR, 0.933; 95% CI, 0.731-1.190). In addition, the frequency of the Q allele was not related to type 2 diabetes (OR, 0.911; 95% CI, 0.630-1.319) or obesity (OR, 0.962; 95% CI, 0.767-1.205). We concluded that the *ENPP1* 121Q allele is not a critical determinant for either diabetes or obesity in Korean males. The discordance between the results of this study and those derived from studies of Dominican, South Asian, Caucasian, Finnish, and French populations might be due to differences in genetic backgrounds between these populations.

Key Words : *Diabetes Mellitus, Type 2; Obesity; Ectonucleotide Pyrophosphatase Phosphodiesterase 1; Association*

Hyun-Ju Seo, Soo-Geun Kim*, and Oh-Joong Kwon†

Department of Public Health, Graduate School of Korea University, Seoul; Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital*, Seoul; Biosewoom Institute of Bioscience & Biotechnology†, Seoul, Korea

Received : 7 June 2007
Accepted : 17 November 2007

Address for correspondence
Soo-Geun Kim, M.D.
Department of Occupational Medicine, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, 108 Pyung-dong, Jongno-gu, Seoul 110-746, Korea
Tel : +82.2-2001-2445, Fax : +82.2-2001-2650
E-mail : ksg6201@empal.com

*This study was supported by Radiation Health Research Institute.

INTRODUCTION

Diabetes decreases the overall life expectancy and cause a heavy burden on public health (1). Moreover, the Asia-pacific region is considered to be on the verge of an emerging diabetes epidemic (2).

The development of type 2 diabetes is affected by genetic and environmental determinants (3). Recently, one study investigated whether common variants of functional and positional candidate genes, including *ADRB3*, *PPARG*, *ENPP1* and *CAPN10*, were determinants of type 2 diabetes (4).

ENPP1, also called K121Q, has a glutamine substitution for lysine at codon 121 (5). Type 2 diabetes is characterized by insulin resistance (6), and *ENPP1* plays an important role in insulin resistance (7, 8). ENPP1 interacts with α-subunit of the insulin receptor to interrupt signaling (9).

In previous studies, the K121Q polymorphism of the human PC-1 gene was strongly associated with insulin resistance (1, 3, 7, 10-12). However, there was no association between insulin resistance and the K121Q variant (13, 14).

In addition, there were discrepancies for the impact of *ENPP1* polymorphism on obesity between ethnic groups (5, 10, 13, 15-19).

Obesity increases the concentration of insulin in plasma and is the major contributor of insulin resistance (20). Obesity appears to be an effect modifier of type 2 diabetes in D1057 carriers (21). The association of obesity with the genetic variant of the insulin receptor substrate was identified in other studies (21, 22). In the Chinese Han population, the PC-1 Q121 allele was associated with insulin resistance. In women, carriers of the Q allele had an increased risk for obesity development (3). In Caucasians and African-Americans, 121Q carriers had an association with increased body mass index (BMI) (23), and the three-allele risk type haploid QdelTG with the Q allele increased the risk for obesity (24). However, in the Danish population, there were no differences in the distribution of frequencies of dominant types (KK wild type and KQ/QQ variant type) and alleles (19).

The complexity of type 2 diabetes is related to factors such as genetic heterogeneity, interactions between genes, and the modulating role played by the environment (4).

In spite of these limitations, studies of type 2 diabetes and genetic factors of obesity can predict the risks for development of both type 2 diabetes and obesity in order to assist primary prevention, and Korea is an appropriate country for such studies because of the homogeneity of racial composition and lifestyle (25).

Therefore, the aim of this study was to analyze the pres-

ence of the *ENPP1* polymorphism, not studied yet in Korean population, to identify the association between genotypes and allele with type 2 diabetes and obesity.

MATERIALS AND METHODS

Subjects

Subjects included 1,945 male workers working for Korea Hydro & Nuclear Power company. This company is an electric power company located at Kori, Yonggwang, Ulchin, Wolsung, and Seoul in Korea.

There were 195 male workers (age 48.2±6.7 yr, BMI 24.67±2.64 kg/m^2) who were diagnosed as diabetics during medical examinations conducted from March 2004 to October. The 1,750 male workers (age 45.2±7.7 yr, BMI 24.77±2.64 kg/m^2) in the control group were selected randomly. We obtained information on the history of diabetes through self-reported questionnaires.

Subjects were included if they met one of the criteria below and their onset age was older than 20 yr old to exclude type 1 diabetes: 1) blood-sugar level before a meal exceeded 126 mg/dL twice or more; 2) blood-sugar level before a meal exceeded 126 mg/dL once or more and blood-sugar level two hours after a meal exceeded 200 mg/dL; 3) those who reported that he had a history of diabetes in the questionnaire and being taken oral hypoglycemic agents.

The workers included in the obesity group were those whose BMI was 25 kg/m^2 or more.

After collecting a blood sample from vein in fasting (≥8 hr) status, we measured the blood-sugar level, insulin, and lipid profile. We also measured height and weight to calculate BMI. If fasting glucose levels were greater than 126 mg/dL, we checked the 2 hr post-prandial plasma glucose level at each site within 1 month. Height and weight were measured by autoanalyzer (Health Guard, Fanics, Seoul, Korea). The fasting blood level was analyzed by glucose-oxidase assay using an autochemistry analyzer. To determine the lipid profile, total cholesterol was analyzed by enzyme assay using cholesterol oxidase (COD), high density lipoprotein (HDL) cholesterol by glycerol phosphate oxidase assay, low density lipoprotein (LDL) cholesterol by direct surfactant assay.

We carried out this study under the approval by the Ethnics Committee of the Asan Medical Center, and obtained written consent from all subjects, providing subjects with sufficient explanation to obtain informed consent.

DNA extraction and PCR

We extracted genomic DNA from buffy coats using the GENErALL™ Blood SV kit (General Biosystem, Seoul, Korea) and following the instructions suggested by the manufacturer. The method of genotyping used to identify the K121Q polymorphism in *ENPP1* exon 4 was polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), using DNA treated with a restriction enzyme after PCR, based on the paper reported by Abate et al. (26).

Statistical analysis

We carried out Student's t-test to analyze the effects of genotypes on biochemical parameters using genotypes as factors. The Hardy-Weinberg equilibrium was computed based on the χ^2 goodness-of-fit test.

We also investigated the differences in frequencies of genotypes between type 2 diabetic and normal groups, and between obesity and normal groups by Fisher's exact test. Associations were considered statistically significant at the $p<0.05$ level. The SPSS 12.0 (for window) statistical software pack-

Table 1. Biochemical parameters of type 2 diabetic and non-diabetic subjects by genotypes of *ENPP1*

	Type 2 diabetics			Non-diabetics		
	KK (n=164)	KQ+QQ (n=31)	p*	KK (n=1,433)	KQ+QQ (n=317)	p*
Age (yr)	48.3±6.5	47.4±7.7	0.48	45.1±7.7	45.6±7.5	0.32
BMI (kg/m^2)	24.6±2.7	24.8±2.5	0.75	24.1±2.7	23.9±2.8	0.23
SBP (mmHg)	130.4±14.0	132.0±18.6	0.64	127.2±15.4	127.0±15.3	0.86
DBP (mmHg)	84.1±10.3	85.1±12.0	0.63	81.4±10.8	81.2±10.6	0.78
FP glucose (mg/dL)	151.0±49.9	160.4±46.8	0.34	90.8±18.2	91.1±18.5	0.79
Total cholesterol (mg/dL)	211.3±40.4	211.5±42.3	0.98	201.6±38.3	200.6±38.2	0.67
HDL cholesterol (mg/dL)	48.4±12.7	45.5±14.6	0.25	50.8±13.2	50.7±13.7	0.96
LDL cholesterol (mg/dL)	130.7±34.2	132.0±37.9	0.85	126.3±31.3	123.3±32.2	0.12
Triglycerides (mg/dL)	187.6±155.4	182.5±108.3	0.86	141.7±86.7	141.3±114.7	0.94
CRP (mg/dL)	0.3±0.2	0.3±0.2	0.22	0.3±0.3	0.4±0.4	0.29
HOMA-IR	0.4±0.6	0.5±0.5	0.55	0.1±0.7	0.1±0.7	0.23

*Unpaired two-tailed Student's t-test.

The skewed HOMA-IR was transformed to natural logarithms to remove skewness.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FP, fasting glucose, CRP, C-reactive protein; HOMA-IR, Homeostasis Model Assessment: estimate of insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein.

age was used for statistical analysis.

RESULTS

The frequencies of the KK type, KQ type, and QQ type in *ENPP1* K121Q were 82.1%, 17% and 0.9%, respectively. The homozygous type of Q carrier (QQ type) was added to the heterozygous type (KQ type) because the frequency of QQ type was very low (0.9%).

We investigated the differences in age, blood pressure, BMI, and results of clinical examinations according to genotypes of *ENPP1* K121Q between the type 2 diabetic and non-diabetic groups (Table 1).

When type 2 diabetics and non-diabetics were pooled (n=1,945), there were no significant differences in BMI, systolic pressure, diastolic pressure, glucose value in fasting status, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, C-reactive protein, and HOMA-IR between the KK type and KQ+QQ type. In addition, there were no significant differences in the same characteristics above between type 2 diabetic group and non-diabetic groups (Table 1), and between the obese group and non-obese groups (Table 2).

The frequencies of genotypes were in accordance with the Hardy-Weinberg equilibrium (p=0.85). The odds ratio of having a KQ+QQ genotype was 0.85 for diabetics versus non-diabetics. The odds ratio of having a Q allele was 0.91 for diabetics versus non-diabetics. However, there was no significant difference in the genotypic and allelic distribution between type 2 diabetics and non-diabetics (Table 3). The odds of a KQ+QQ genotype were 0.93 for obese versus non-obese subjects. Furthermore, the odds of having a Q allele were 0.96 for obese versus non-obese subjects. However, there was no significant difference in the genotypic and allelic distribution between obese and non-obese (Table 4). The frequency of the KK type in *ENPP1* K121Q genotypes was 82.1%, that of KQ+QQ type was 17.9% and that of Q allele was 9.4%. There was no statistically significant difference in the distribution among these genotypes and alleles (p=0.81, p=0.89, respectively), although the 121Q carrier and Q allele in obese and/or diabetics seemed to differ slightly from those in the non-obese non-diabetics (reference group).

Table 2. Biochemical parameters of obese and non-obese subjects according to genotypes of *ENPP1*

	Obese subjects			Non-obese subjects		
	KK (n=576)	KQ+QQ (n=120)	p*	KK (n=1,021)	KQ+QQ (n=228)	p*
Age (yr)	46.3±7.8	46.2±7.3	0.91	44.9±7.6	45.5±7.6	0.33
BMI (kg/m^2)	26.9±1.8	26.9±1.9	0.70	22.6±1.7	22.5±1.8	0.30
SBP (mmHg)	132.2±15.5	131.6±15.5	0.67	124.8±14.5	125.3±15.3	0.67
DBP (mmHg)	84.9±10.9	84.1±10.2	0.49	79.8±10.3	80.2±10.8	0.67
FP glucose (mg/dL)	101.6±32.5	104.8±35.9	0.34	94.3±27.8	93.3±25.3	0.59
Total cholesterol (mg/dL)	209.0±38.2	210.3±42.6	0.75	198.9±38.4	196.9±35.7	0.47
HDL cholesterol (mg/dL)	48.3±12.3	46.4±12.1	0.11	51.8±13.5	52.3±14.3	0.59
LDL cholesterol (mg/dL)	131.7±31.5	128.3±36.2	0.29	123.9±31.4	121.8±30.8	0.36
Triglycerides (mg/dL)	171.2±115.4	186.1±161.4	0.34	132.4±81.7	123.3±71.1	0.12
CRP (mg/dL)	0.3±0.2	0.4±0.5	0.08	0.4±0.3	0.3±0.2	0.54
HOMA-IR	0.4±0.6	0.4±0.7	0.81	-0.01±0.7	-0.1±0.6	0.17

*Unpaired two-tailed Student's t-test.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FP, fasting glucose, CRP, C-reactive protein; HOMA-IR, Homeostasis Model Assessment: estimate of insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 3. Frequencies of PC-1 K121Q genotypes according to diabetes

	Genotypes (%)			Alleles (%)		
	KK	KQ+QQ	Total	K	Q	Total
Type 2 diabetics	164 (84.1)	31 (15.9)	195 (100.0)	356 (91.3)	34 (8.7)	390 (100.0)
Non-diabetics	1,433 (81.9)	317 (18.1)	1,750 (100.0)	3,168 (90.5)	332 (9.5)	3,500 (100.0)
Total	1,597 (82.1)	348 (17.9)	1,945 (100.0)	3,524 (90.6)	366 (9.4)	3,890 (100.0)
OR* (95% CI)	0.85 (0.57-1.28)			0.91 (0.63-1.32)		

*Fisher's exact test.

OR, odds ratios; CI, confidence interval.

Table 4. Frequencies of PC-1 K121Q genotypes according to obesity

	Genotypes (%)			Alleles (%)		
	KK	KQ+QQ	Total	K	Q	Total
Obese	576 (82.8)	120 (17.2)	696 (100.0)	1,264 (90.8)	128 (9.2)	1,392 (100.0)
Non-obese	1,021 (81.7)	228 (18.3)	1,249 (100.0)	2,260 (90.5)	238 (9.5)	2,498 (100.0)
Total	1,597 (82.1)	348 (17.9)	1,945 (100.0)	3,524 (90.6)	366 (9.4)	3,890 (100.0)
OR* (95% CI)	0.93 (0.73-1.19)			0.96 (0.77-1.21)		

*Fisher's exact test.

OR, odds ratios; CI, confidence interval.

Table 5. Stratified analysis between allele and diabetes adjusted for obesity

	Allele	Type 2 diabetics	Non-diabetics	Total	OR* (95% CI)
Obese	K	145 (11.5)	1,119 (88.5)	1,264 (100.0)	
	Q	15 (11.7)	113 (88.3)	128 (100.0)	
	Subtotal	160 (11.5)	1,232 (88.5)	1,392 (100.0)	1.095 (0.756-1.585)
Non-obese	K	211 (9.3)	2,049 (90.7)	2,260 (100.0)	
	Q	19 (8.0)	219 (92.0)	238 (100.0)	
	Subtotal	230 (9.2)	2,268 (90.8)	2,498 (100.0)	

*Mantel-Haenszel χ^2 test.
OR, odds ratios; CI, confidence interval.

Table 6. Stratified analysis between allele and obesity adjusted for diabetes

	Allele	Obese	Non-obese	Total	OR* (95% CI)
Type 2 diabetics	K	145 (40.7)	211 (59.3)	356 (100.0)	
	Q	15 (44.1)	19 (55.9)	34 (100.0)	
	Subtotal	160 (41.0)	230 (59.0)	390 (100.0)	1.038 (0.828-1.301)
Non-diabetics	K	1,119 (35.3)	2,049 (64.7)	3,168 (100.0)	
	Q	113 (34.0)	219 (66.0)	332 (100.0)	
	Subtotal	1,232 (35.2)	2,268 (64.8)	3,500 (100.0)	

*Mantel-Haenszel χ^2 test.
OR, odds ratios; CI, confidence interval.

In determining the prevalence of the Q allele carriers (KQ and QQ subjects) and Q allele, there were no significant differences in the genotypic and allelic distribution with the respect to any phenotypes (data not shown).

After adjusting for the effects of obesity, the probability of type 2 diabetes in KQ+QQ type was 0.858 (data not shown) and that in Q allele was 1.095, showing no significant difference (Table 5). Moreover, after adjusting for the effects of type 2 diabetes, the probability of developing obesity in the KQ+QQ type was 0.936 (data not shown) and that in the Q allele was 1.038, showing no significant difference (Table 6).

DISCUSSION

The results of studies of the association between *ENPP1* K121Q variants and both type 2 diabetes and obesity in several races are disparate. We carried out this study to investigate the association of K121Q variants with type 2 diabetes and obesity in Korean male workers.

Insulin resistance is a major component of the pathogenesis of type 2 diabetes (27), and insulin receptor kinase activity is impaired in muscle and other insulin-sensitive tissue of many type 2 diabetic patients (28), and then a potential inhibitor of the insulin receptor tyrosine kinase is identified as the plasma-cell membrane differentiation antigen-1 (PC-1) (29). Therefore, it is significant to analyze *ENPP1* (PC-1) polymorphism.

In the previous studies of the association between type 2 diabetes and polymorphism in *ENPP1*, the K121Q missense mutation increased the odds ratio (OR) for type 2 diabetes in Dominican (10), South Asian, Caucasian (16), Finnish (18), and French populations (24). Moreover, according to a meta-analysis of the association between *ENPP1* K121Q variant and type 2 diabetes, the odds ratios were 1.30 (95% confidence interval [CI], 1.13-1.50) (16) and 1.17 (95% CI, 1.10-1.25) (19), showing significant association. In this study, 121Q was not associated with type 2 diabetes, showing consistent results with those in the Japanese population (5), Danish Caucasians (13), Oji-Cree population (17), Finnish population (18), and Danish white subjects (19). Most type 2 diabetes in Koreans is characterized by non-obesity, thus the *ENPP1* K121Q mutant relevant to insulin resistance possibly could be a candidate gene that is not appropriate to explain susceptibility to type 2 diabetes. This can be a possible explanation for the lack of association between *ENPP1* 121Q carrier and type 2 diabetes in this study.

Obesity is a main risk factor for the development of type 2 diabetes (20) and there is linear association between obesity and type 2 diabetes (3). In previous studies of the association between obesity and polymorphism in *ENPP1*, 121Q carriers and/or Q allele were associated with obesity in the Chinese Han population (BMI of obesity group $\geq$27 kg/m^2) (3), Caucasians (BMI of obesity group >90th percentile), African-American adults (BMI of obesity group >80th percentile) (23), French population (BMI of obesity group $\geq$95th percentile) (24), and Dominican population (BMI of obesity group $\geq$30 kg/m^2) (10). However, in this study (BMI of obesity group $\geq$25 kg/m^2), there was no difference in distribution between obesity and 121Q carriers and presence of the Q allele. This result was consistent with those from a study of 7,333 Danes (19) and a Spanish population (14) in which the BMI of the obesity group was 25 kg/m^2 or higher. On the other hand, in Matsuoka's study, K121 was associated with an increased BMI (23). In this study, the percentage of subjects whose BMI was 30 kg/m^2 or higher was too low (2.5%) to investigate the effect of K121Q genotype on

obesity.

The results of the present study showed that the frequencies of the Q allele was 8.7% in the type 2 diabetic group and 9.2% in the obesity group, which was lower than those in Finnish and Swedish populations (12.9-15.1%) (11), Danish Caucasians (14-16%) (13), South Asians in Chennai (14 %), Caucasians in Dallas (16%), South Asians in Dallas (19%) (16), the Dominican population (54.2%) (10) and, Black children (77%) (30). The frequencies of the Q allele investigated in this study might have a smaller statistical power to explain any association with either type 2 diabetes or obesity with 121Q carriers (KQ+QQ) and/or the Q allele.

In conclusion, the present study suggests that the *ENPP1* K121Q polymorphism was not associated with type 2 diabetes and obesity. The results of negative associations in this study might be attributable to the low prevalence of obesity, relatively younger age, and low frequencies of the 121Q carriers. Large and prospective studies are needed to confirm this preliminary observation in the Korean population.

REFERENCES

1. Klein R. *Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 1995; 18: 258-68.*
2. Amos AF, McCarty DJ, Zimmet P. *The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 1997; 14 (Suppl 5): S1-85.*
3. Wan C, Zhang T, Wang B, Han Y, Zhang C, Zhang Y, Gong H, Jin F, Wang L. *Obesity risk associated with the K121Q polymorphism of the glycoprotein PC-1 gene. Diabetes Obes Metab 2006; 8: 703-8.*
4. Busch CP, Hegele RA. *Genetic derminants of type 2 diabetes mellitus. Clin Genet 2001; 60: 243-54.*
5. Keshavarz P, Inoue H, Sakamoto Y, Kunika K, Tanahashi T, Nakamura N, Yoshikawa T, Yasui N, Shiota H, Itakura M. *No evidence for association of the ENPP1 (PC-1) K121Q variant with risk of type 2 diabetes in a Japanese population. J Hum Genet 2006; 51: 559-66.*
6. Kahn BB, Flier JS. *Obesity and insulin resistance. J Clin Invest 2000; 106: 473-81.*
7. Pizzuti A, Frittitta L, Argiolas A, Baratta R, Goldfine ID, Bozzali M, Ercolino T, Scarlato G, Iacoviello L, Vigneri R, Tassi V, Trischitta V. *A polymorphism (K121Q) of the human glycoprotein PC-1 gene coding region is strongly associated with insulin resistance. Diabetes 1999; 48: 1881-4.*
8. Goldstine ID, Maddux BA, Youngren JF, Trischitta V, Frittitta L. *Role of PC-1 in the etiology of insulin resistance. Ann N Y Acad Sci 1999; 892: 204-22.*
9. Maddux BA, Goldfine ID. *Membrane glycoprotein PC-1 inhibition of insulin receptor function occurs via direct interaction with the receptor alpha-subunit. Diabetes 2000; 49: 13-9.*
10. Hamaguchi K, Terao H, Kusuda Y, Yamashita T, Hazoury Bahles JA, Cruz LL M, Brugal V LI, Jongchong WB, Yoshimatsu H, Sakata T. *The PC-1 Q121 allele is exceptionally prevalent in the Dominican Republic and is associated with Type 2 Diabetes. J Clin Endocrinol Metab 2004; 89: 1359-64.*
11. Gu HF, Almgren P, Lindholm E, Frittitta L, Pizzuti A, Trischitta V, Groop LC. *Association between the human glycoprotein PC-1 gene and elevated glucose and insulin levels in a paired-sibling analysis. Diabetes 2000; 49: 1601-3.*
12. Kubaszek A, Pihlajamäki J, Karhapää P, Vauhkonen I, Laakso M. *The K121Q polymorphism of the PC-1 gene is associated with insulin resistance but not with dyslipidemia. Diabetes Care 2003; 26: 464-7.*
13. Rasmussen SK, Urhammer SA, Pizzuti A, Echwald SM, Ekstrøm CT, Hansen L, Hansen T, Borch-Johnsen K, Frittitta L, Trischitta V, Pedersen O. *The K121Q variant of the human PC-1 gene is not associated with insulin resistance or type 2 diabetes among Danish Caucasians. Diabetes 2000; 49: 1608-11.*
14. González-Sánchez JL, Martínez-Larrad MT, Fernández-Pérez C, Kubaszek A, Laakso M, Serrano-Ríos M. *K121Q PC-1 gene polymorphism is not associated with insulin resistance in a Spanish population. Obes Res 2003; 11: 603-5.*
15. Bacci S, Ludovico O, Prudente S, Zhang YY, Di Paola R, Mangiacotti D, Rauseo A, Nolan D, Duffy J, Fini G, Salvemini L, Amico C, Vigna C, Pellegrini F, Menzaghi C, Doria A, Trischitta V. *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. Diabetes 2005; 54: 3021-5.*
16. Abate N, Chandalia M, Satija P, Adams-Huet B, Grundy SM, Sandeep S, Radha V, Deepa R, Mohan V. *ENPP1/PC-1 K121Q polymorphism and genetic susceptibility to type 2 diabetes. Diabetes 2005; 54: 1207-13.*
17. Hegele RA, Harris SB, Zinman B, Hanley AJ, Cao H. *Absence of association of type 2 diabetes with CAPN 10 and PC-1 polymorphisms in Oji-Cree. Diabetes Care 2001; 24: 1498-9.*
18. Laukkanen O, Pihlajamäki J, Lindström J, Eriksson J, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Tuomilehto J, Uusitupa M, Laakso M; Finnish Diabetes Prevention Study Group. *Common polymorphism in the genes regulating the early insulin signaling pathway: effects on weight change and the conversion from impaired glucose tolerance to type 2 diabetes. The Finnish diabetes prevention study. Diabetologia 2004; 47: 871-7.*
19. Grarup N, Urhammer SA, EK J, Albrechtsen A, Glümer C, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O. *Studies of the relationship between the ENPP1 K121Q polymorphism and type 2 diabetes, insulin resistance and obesity in 7,333 Danish white subjects. Diabetologia 2006; 49: 2097-104.*
20. Kopelman PG. *Obesity as a medical problem. Nature 2000; 404: 635-43.*
21. Clausen JO, Hansen T, Bjørbaek C, Echwald SM, Urhammer SA, Rasmussen S, Anderson CB, Hansen L, Almind K, Winther K, Haraldsdottir J, Borch-Johnsen K. *Insulin resistance: interaction between obesity and a common variant of insulin receptor substrate-1. Lancet 1995; 346: 397-402.*
22. Sigal RJ, Doria A, Warram JH, Krolewski AS. *Codon 972 polymorphism in the insulin receptor substrate-1 gene, obesity, and risk of noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab*

1996; 81: 1657-9.

23. Matsuoka N, Patki A, Tiwari HK, Allison DB, Johnson SB, Gregersen PK, Leibel RL, Chung WK. *Association of K121Q polymorphism in ENPP1 (PC-1) with BMI in Caucasian and African-American adults. Int J Obes (Lond) 2006; 30: 233-7.*
24. Meyre D, Bouatia-Naji N, Tounian A, Samson C, Lecoeur C, Vatin V, Ghoussaini M, Wachter C, Hercberg S, Charpentier G, Patsch W, Pattou F, Charles MA, Tounian P, Clément K, Jouret B, Weill J, Maddux BA, Goldfine ID, Walley A, Boutin P, Dina C, Froguel P. *Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. Nat Genet 2005; 37: 863-7.*
25. Park JH. *Candidate Gene Approach for the Genetics of Type 2 Diabetes Mellitus. J Korean Diabetes Assoc 1998; 22: 439-41.*
26. Abate N, Carulli L, Cabo-Chan A Jr, Chandalia M, Snell PG, Grundy SM. *Genetic polymorphism PC-1 K121Q and ethnic susceptibility to insulin resistance. J Clin Endocrinol Metab 2003; 88: 5927-34.*
27. Pedersen O. *Genetics of insulin resistance. Exp Clin Endocrinol Diabetes 1999; 107: 113-8.*
28. Häring H, Obermaier-Kusser B. *Insulin receptor kinase defects in insulin-resistant tissues and their role in the pathogenesis of NIDDM. Diabetes Metab Rev 1995; 5: 431-41.*
29. Maddux BA, Sbraccia P, Kumakura S, Sasson S, Youngren J, Fisher A, Spencer S, Grupe A, Henzel W, Stewart TA, Reaven GM, Goldfine ID. *Membrane glycoprotein PC-1 and insulin resistance in non-insulin-dependent diabetes mellitus. Nature 1995; 373: 448-51.*
30. Morrison JA, Gruppo R, Glueck CJ, Stroop D, Fontaine RN, Wang P, Smith KL. *Population-specific alleles: the polymorphism (K121Q) of the human glycoprotein PC-1 gene is strongly associated with race but not with insulin resistance in black and white children. Metabolism 2004; 53: 465-8.*