**Original Article**

# *ENPP1/PC-1* Gene K121Q Polymorphism Is Associated with Obesity in European Adult Populations: Evidence from A Meta-Analysis Involving 24 324 Subjects

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**Abstract**

**Objective** Findings from the previous studies have suggested a relationship between ectonucleotide pyrophosphatase /phosphodiesterase 1 (*ENPP-1*) or plasma cell membrane glycoprotein 1 (*PC-1*) gene single nucleotide polymorphism (K121Q, rs1044498) and genetic susceptibility to obesity. However, such relationship is not reproduced by some currently available studies. In this context, the present study is aimed to quantitatively analyze the association of K121Q variant with obesity in all published case-control studies in European adult populations.

**Methods** Published literature from PubMed, EMBASE, and ISI web of science databases were retrieved. The studies evaluating the association of *ENPP1/PC1* gene K121Q polymorphism with obesity were included, in which sufficient data were presented to calculate the odds ratio (OR) with 95% confidence intervals (CIs).

**Results** Ten case-control studies meeting the inclusion criteria identified a total of 24,324 subjects including 11,372 obese and 12,952 control subjects. The meta-analysis results showed a statistically significant association of K121Q with obesity [OR (95%CI): 1.25 (1.04-1.52) *P*=0.021] under a recessive model of inheritance (QQ *vs*. KK+KQ) without heterogeneity or publication bias.

**Conclusions** The results from the present study have indicated that *ENPP1/PC1* Q121 variant may increase the risk of obesity and that more well-designed studies based on a larger population will be required to further evaluate the role of *ENPP1/PC1* gene K121Q polymorphism in obesity and other related metabolic syndromes.

**Key words**: Ectonucleotide pyrophosphatase /phosphodiesterase 1 (*ENPP1*); Plasma cell membrane glycoprotein 1 (*PC1*); K121Q; Single nucleotide polymorphism (SNP); Obesity

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## INTRODUCTION

Over the recent years, the incidence of obesity has been increasing worldwide. More than one billion people are now classified as overweight or obese[1-2]. There are many adverse consequences associated with obesity, such as cardiovascular disease, type 2 diabetes, and decreased average life expectancy[3-4]. Although it was generally accepted that this metabolic disorder is mainly due to an abnormal lifestyle, the genetic factors are found to play a vital role in predisposing individuals to obesity. Exciting progress has recently been made in elucidating the underlying molecular mechanisms of obesity, which has expanded our knowledge and provided new clues to the prevention and treatment of this metabolic syndrome[5-7].

Obesity is a multifactorial and polygenicdisorder. Many monogenic forms of obesity have been identified by candidate gene approaches. Recently, genome-wide association studies (GWAS) are emerging as a major tool to identify obesity-susceptible genes and loci[8]. These associations have been confirmed in a wide range of populations with different genetic backgrounds, although the underlying mechanisms remain to be elucidated.

Ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP-1*), also known as plasma cell membrane glycoprotein 1 (*PC-1*), is a member of the ENPP gene family. The encoded protein is a type II transmembrane glycoprotein that has broad specificity and cleaves a variety of substrates, including phosphodiester bonds of nucleotides and nucleotide sugars and pyrophosphate bonds of nucleotides and nucleotide sugars. ENPP1 downregulates insulin signaling by inhibiting the tyrosine kinase activity of insulin receptor, resulting in reduced insulin sensitivity[9]. ENPP1 is a candidate protein that may play a role in insulin resistance and type 2 diabetes by its overexpression and/or overactivity[10]. About a decade ago, *ENPP1* gene was reported to have a single nucleotide polymorphism (SNP) where a lysine (K) was substituted by a glutamine (Q) at codon 121 (K121Q; rs1044498). A comprehensive meta-analysis has recently shown that *ENPP1* Q121 variant modestly increases the risk of type 2 diabetes, and the effect appears to be modulated by body mass index (BMI)[11]. Considering the major role of obesity in deteriorating glucose homeostasis[12], it is necessary to identify whether *ENPP1* K121Q variant is associated with obesity. However, up to now the association of *ENPP1* gene K121Q polymorphism with obesity has been controversial for a number of reasons including insufficient statistical power, recruitment procedures of the study population, and differences in the genetic and environmental backgrounds[13]. Many studies including ours[14-16] have reported on the effect of ethnic differences on genetic predisposition to human diseases. Most studies on the association of *ENPP1* with obesity have been conducted in European adult populations. This study, therefore, is aimed to quantitatively analyze the association of *ENPP1* gene K121Q polymorphism with genetic predisposition to obesity in all available published case-control studies in European adult populations.

## MATERIALS AND METHODS

### *Literature and Search Strategy*

The literature databases including PubMed (1950 to 2010), EMBASE (1966 to 2010) and ISI web of science (1975 to 2010) were searched. These databases included journal articles, degree dissertations and abstracts of scientific conferences.

A search strategy to identify all possible studies was employed by combining the following Medical Subject Headings (MeSH) terms and other relevant words:

(1) ectonucleotide pyrophosphatase/phosphordiesterase 1/*ENPP1*/*ENPP*/*NPP1*/*NPP*;

(2) phosphodiesterase I/nucleotide pyrophosphatase 1/*PDNP1*/*PDNP*;

(3) plasma-cell membrane glycoprotein 1/*PC1*/*PC-1*;

(4) K121Q/Lys121Gln;

(5) SNP/polymorphism/variant/variation/mutation;

(6) body mass index (BMI);

(7) obese /obesity.

The full-text papers of potential relevant studies were retrieved and carefully reviewed.

### *Inclusion Criteria and Data Extraction*

The studies used for meta-analysis were obliged to meet all the following inclusion criteria: (1) evaluating the association of *ENPP1* gene K121Q polymorphism with obesity; (2) case-control design; (3) European adult populations (“Whites” or

"Caucasians" populations of European ancestry based on grandparental country of origin.); (4) sufficient data for K121Q genotype presented to calculate the odds ratio (OR) with confidence interval (CI). For each study, the following information was extracted: (1) name of the authors; (2) year of publication; (3) country and ethnicity of the population studied; (4) the characteristics and selection criteria of the subjects; (5) number of cases and controls; (6) OR and 95% CI.

The authors independently assessed the articles for inclusion/exclusion, and reached consensus by resolving disagreements.

### *Statistical Analysis*

The deviation from Hardy-Weinberg equilibrium (HWE) for distribution of the allele frequencies was analyzed by Fisher's exact test. The association of *ENPP1* gene K121Q polymorphism with obesity was estimated by calculating pooled ORs. The significance of the pooled ORs was determined by *Z* test ($P<0.05$ was considered statistically significant). $I^2$-based Q statistic test was performed to evaluate the variation that was due to heterogeneity rather than by chance. A random- (DerSimonian-Laird method[17]) or fixed- (Mantel-Haenszel method[18]) effects model was used to calculate pooled effect estimates in the presence ($P \le 0.10$) or absence ($P>0.10$) of heterogeneity, respectively. Publication bias was assessed by Egger's test[19] ($P<0.05$ was considered statistically significant). Subgroup analyses (population-based or hospital-based) were performed to examine the potential bias from the recruitment of the subjects. To evaluate the stability of the results, sensitivity analysis was performed. In this analysis, after removing some potential outliers, the overall homogeneity and effect size were calculated. Data analysis was performed using STATA version 10 (StataCorp LP, College Station, Texas, USA).

## RESULTS

### *Characteristics of the Included Studies*

The literature search identified a total of 174 potential relevant studies. The full texts of selected articles were retrieved and carefully reviewed to assess the eligibility according to the inclusion criteria. Ten case-control studies meeting the inclusion criteria[20-29] identified a total of 24 324 subjects, including 11 372 case and 12 952 control subjects. The selected studies were published between 2005 and 2009. The deviation from HWE for distribution of the allele frequencies was analyzed by Fisher's exact test. No significant deviation from HWE was observed. The similarity of the recruitment criteria and genotyping protocols ensured that the studies were of high homogeneity which enabled us to perform the meta-analysis and minimized potential errors. The characteristics of the included studies are listed in Table 1.

### *Meta-analysis Results*

Under an allelic model (Q allele *vs*. K allele), the meta-analysis result showed no significant effect of K121Q genotype on the risk of obesity [OR (95%CI): 1.03 (0.96-1.11), $P=0.379$], with moderate heterogeneity ($P=0.096$). The forest plot is shown in Figure 1a. Under a dominant genetic model (QQ+KQ *vs*. KK), it showed no significant effect of K121Q on the risk for obesity [OR (95%CI): 1.03 (0.92-1.16), $P=0.583$] with significant evidence of heterogeneity ($P=0.038$). The forest plot is shown in Figure 1b. By contrast, under a recessive model of inheritance (QQ *vs*. KK+KQ), the association of K121Q with obesity was statistically significant [OR (95%CI): 1.25 (1.04-1.52), $P=0.021$], without heterogeneity ($P=0.554$). The forest plot is shown in Figure 1c.

In addition, a subgroup meta-analysis stratified by study design (hospital-based or population-based) was conducted under a recessive model of inheritance (Figure 2). The association of K121Q with obesity was stronger [OR (95%CI): 1.33 (1.05-1.69), $P=0.020$] in hospital-based studies[20-22,26,28] than that in population-based studies [OR (95%CI): 1.13 (0.82-1.56), $P=0.462$][23,25,27]. There was no significant heterogeneity in either of the subgroups.

In order to test the stability of the result, the meta-analysis was repeated after exclusion of those studies that might be potential outliers, e.g. with morbid obesity (BMI≥40 kg/m$^2$) and it was shown that the results were not influenced by exclusion of potential outliers (data not shown).

### *Potential Publication Bias*

Begg's funnel plot was generated to evaluate the potential publication bias (Figure 3) and no publication bias was detected (Egger's test $P=0.656$).

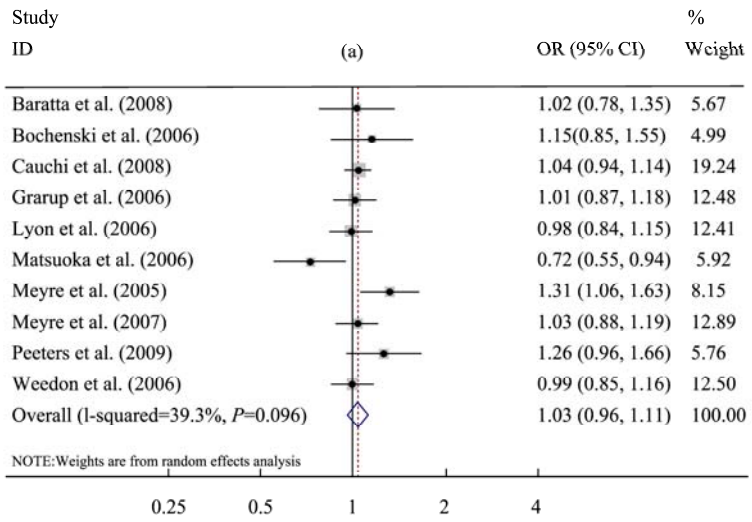
**Table 1.** Characteristics of Studies Included in the Meta-analysis

| Study | Country | Groups | *N* | Sex (M / F) | Age (years) | BMI (kg/m$^2$) | Q Allele Frequency | HWE *P* |
|---|---|---|---|---|---|---|---|---|
| Baratta et al. (2008) | Italy | case | 475 | 127/348 | 37.2±0.5 | ≥30 | 0.169 | 0.592 |
| | | control | 289 | 138/151 | 36.7±0.7 | <30 | 0.166 | 0.663 |
| Bochenski et al. (2006) | Poland | case | 398 | N.A. | N.A. | N.A. | 0.131 | 0.595 |
| | | control | 398 | N.A. | N.A. | N.A. | 0.116 | 0.738 |
| Cauchi et al. (2008) | France and Switzerland | case | 2788 | N.A. | N.A. | ≥30 | 0.156 | 0.014 |
| | | control | 4321 | N.A. | N.A. | <30 | 0.151 | 0.294 |
| Grarup et al. (2006) | Denmark | case | 969 | N.A. | N.A. | ≥30 | 0.131 | 0.884 |
| | | control | 2582 | N.A. | N.A. | <25 | 0.129 | 0.476 |
| Lyon et al. (2006) | USA and Poland | case | 1918 | 886/1032 | 56.5±8.9 | 35.0±3.4 | 0.14 | N.A. |
| | | control | 955 | 439/516 | 56.6±9.4 | 21.5±0.8 | 0.15 | N.A. |
| Matsuoka et al. (2006) | USA | case | 329 | 194/135 | 48.9±9.6 | 38.7±4.8 | 0.175 | 0.008 |
| | | control | 341 | 236/105 | 47.5±11.0 | 21.6±0.5 | 0.227 | 0.619 |
| Meyre et al. (2005) | France | case | 680 | N.A. | 45.8±12.0 | 47.4±7.4 | 0.166 | 0.085 |
| | | control | 623 | N.A. | 50.9±12.7 | 22.9±2.3 | 0.132 | 0.328 |
| Meyre et al. (2007) | France | case | 934 | N.A. | N.A. | ≥30 | 0.159 | 0.118 |
| | | control | 2005 | N.A. | N.A. | <27 | 0.155 | 0.196 |
| Peeters et al. (2009) | Belgium | case | 1078 | 469/609 | 42.6±0.4 | 38.2±0.2 | 0.136 | 0.021 |
| | | control | 323 | 100/223 | 35.9±0.4 | 22.1±0.1 | 0.111 | 0.264 |
| Weedon et al. (2006) | UK | case | 1803 | N.A. | N.A. | ≥30 | 0.135 | N.A. |
| | | control | 1115 | N.A. | N.A. | <25 | 0.135 | N.A. |

***Note***. BMI: body mass index; HWE: Hardy-Weinberg equilibrium; N.A. Not available.

## DISCUSSION

The results of previous studies on the association of *ENPP1* gene K121Q polymorphism with obesity have been controversial. Some studies reported a significant effect of the K121Q polymorphism on the risk of obesity[26] while the others reported no significant correlation between them[20-25,27-29]. The reasons for these discrepancies are not clear. It may be related to a number of factors that vary among different populations, such as environmental exposures (dietary intake and physical activity), other yet unidentified functional SNPs that are in linkage disequilibrium with the K121Q polymorphism, or different genetic backgrounds of the populations studied. In addition, the limited sample size and statistical power may be one of the most likely reasons.



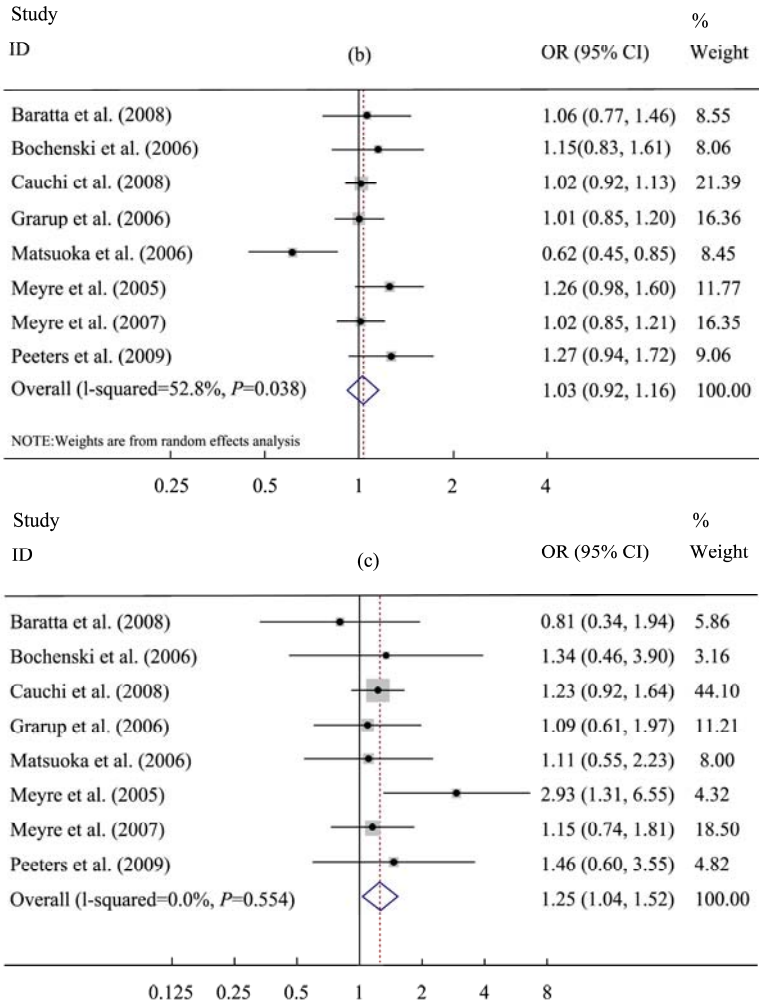



**Figure 1**. Forest plot of the meta-analysis result (a) using a random effects model and an allelic model of inheritance; (b) using a random effects model and a dominant model of inheritance; (c) using a fixed effects model and a recessive model of inheritance.

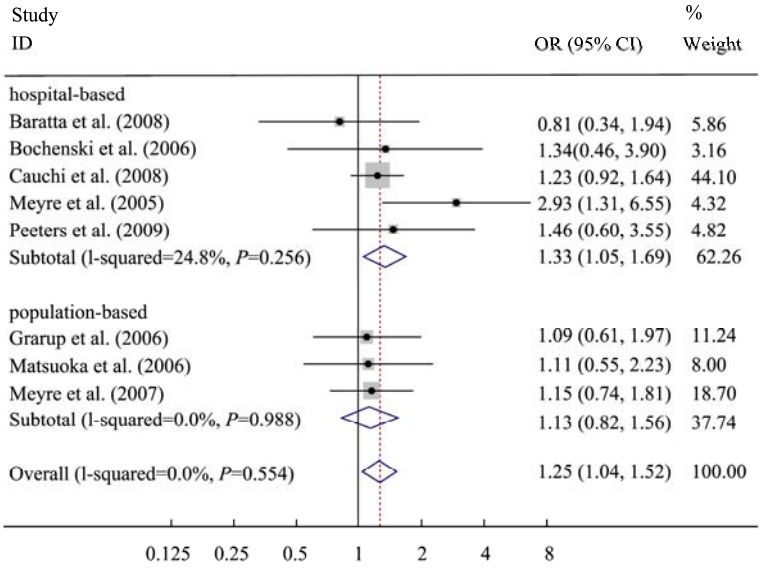



**Figure 2**. Pooled OR using fixed effects meta-analysis stratified by study design: hospital-based or population-based.

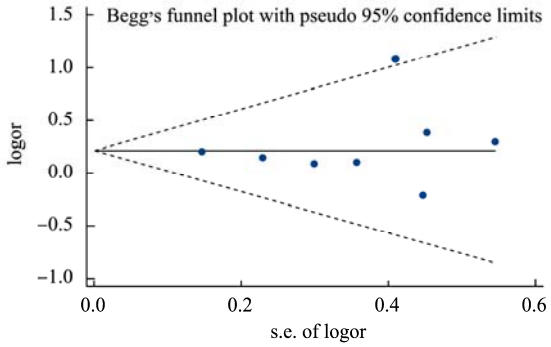



**Figure 3**. Funnel plot of standard error against log OR, using a fixed effects model and a recessive model of inheritance.

The present study was aimed to quantitatively analyze the association of *ENPP1* gene K121Q polymorphism with genetic predisposition to obesity using meta-analysis. Very strict inclusion criteria were applied in this analysis to ensure that only studies of high quality were used for meta-analysis so as to minimize potential errors. Due to the differences in allele frequencies across populations[30], the current meta-analysis used was limited to the subjects of European descent. Ten eligible studies including more than 20 000 subjects met the inclusion criteria. Although the results revealed no significant effect of K121Q genotype on the risk of obesity under the allelic/dominant models, there was evidence for significant association under a recessive model of inheritance [OR (95% CI): 1.25 (1.04-1.52), *P*=0.021]. Only under the recessive model did the meta-analysis result show no publication bias or heterogeneity among the studies, indicating that this model was the best-fit for the data analysis. Moreover, the sensitivity analysis was performed to remove the potential outliers, which further validated the results and strengthened the conclusion.

Many studies, albeit not all, have shown that the K121Q variant is associated with insulin resistance and type 2 diabetes. In addition, obesity has been strongly associated with increased insulin resistance and type 2 diabetes[31-32]. A recent large-scale meta-analysis has reported that the *ENPP1* Q121 variant increases the risk of type 2 diabetes which appears to be modulated by BMI[11]. The deleterious role of the Q121 variant on the risk of type 2 diabetes is observable only among obese patients, rather than among non-obese individuals, suggesting a gene-by-obesity interaction in the risk modulation of type 2 diabetes. However, the mechanism by which *ENPP1* influences obesity has not been clearly studied.

Meta-analysis has a vital advantage compared to individual studies, that is, all the studies available can be pooled together, which dramatically increases the power of statistical analysis. Therefore, the modest effect can be detected more easily. On the other hand, the present meta-analysis does have some limitations. First, the results may be influenced by the recruitment of case (obese) and control subjects, as hospital-based case-control studies for obesity may depend on the presence of diabetes as an inclusion criterion. The authors conducted stratified analyses according to the study design. Meta-analysis of the three population-based studies[23,25,27] was performed. A trend was observed that Q allele carriers might have a higher risk of obesity. However, no definite conclusion can be drawn because of limited sample size (only 2 232 obese subjects). Meta-analysis of five hospital-based studies[20-22,26,28] (which included mostly diabetic patients) showed that Q121 variant was significantly associated with the risk of obesity. These results indicated that the strength of association could be driven by the high glycemic status because of repeatedly reported interaction between the Q121 variant and obesity in increasing the risk of type 2 diabetes[11]. Second, obesity was not defined by uniform criteria in all studies. In some studies, the subjects above the 90th percentile for BMI were selected as obese cases, while in other ones, the median value of % ideal body weight was used as cut-off point to define cases and controls; in more other studies, morbidly obese patients with BMI values equal or above 40 kg/m$^2$ were included. To address the concerns of lack of uniformity, a meta-analysis excluding each of these studies was also performed (data not shown). The conclusion remained as it was: K121Q polymorphism is associated with obesity under a recessive model of inheritance. Third, the meta-analysis was based on the studies with incomplete information available. A more precise analysis could have been performed if additional confounding factors (e.g. gender, age, dietary habit, and lifestyle) were taken into account. The result of the present meta-analysis, therefore, should be interpreted with caution. Multi-centered, large-population and well-designed epidemiologic studies are required to further evaluate the role of *ENPP1* gene K121Q polymorphism in genetic predisposition to obesity.

In summary, the present research indicates that the *ENPP1* Q121 variant increases the risk of obesity

the under a recessive model of inheritance. Considering the increasing prevalence of obesity and related diseases worldwide, our findings may have important clinical and public health implications. More epidemiological and mechanistic studies are necessary to further elucidate the role of *ENPP1* gene K121Q polymorphism in obesity and other metabolic syndromes.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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