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ENPP1 K121Q polymorphism and type 2 diabetes mellitus in the Chinese population: a meta-analysis including 11 855 subjects

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ARTICLE INFO

Article history:
Received 13 July 2011
Accepted 5 October 2011

ABSTRACT

Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (*ENPP1*) K121Q gene polymorphism has been suggested to be associated with the increased risk of developing type 2 diabetes mellitus (T2D), but relevant research results are still contradictory. To explore the relationship between *ENPP1* K121Q gene polymorphism and T2D in the Chinese population, a meta-analysis was performed. Fourteen independent studies involving 11 855 subjects were retrieved from electronic databases. The pooled odds ratio (ORs) for the distribution of Q allele frequency of the *ENPP1* K121Q gene and its corresponding 95% confidence interval (95% CI) were assessed using a random-effects model. Under an allelic model of inheritance, the distribution of Q allele frequency was 0.107 for the T2D group and 0.093 for the control group. The pooled OR for the distribution of Q allele frequency of *ENPP1* K121Q gene was 1.29 (95% CI, 1.09-1.53; $P_{heterogeneity} = .006$; $I^2 = 55.6\%$). There was a significant association between *ENPP1* K121Q gene polymorphism and T2D in the Chinese population ($P = .003$). Under a dominant model of inheritance, the KQ + QQ/KK value was 0.259 for the T2D group and 0.220 for the control group. The pooled OR for the KQ + QQ/KK value was 1.51 (95% CI, 1.20-1.91; $P_{heterogeneity} < .0001$; $I^2 = 71.8\%$). The association between *ENPP1* K121Q gene polymorphism and T2D in the Chinese population followed a dominant model of inheritance ($P = .0005$). In the Chinese population, the *ENPP1* K121Q gene polymorphism was implied to be involved with T2D susceptibility. People with the Q allele of the *ENPP1* K121Q gene might be predisposed to T2D.

1. Introduction

Type 2 diabetes mellitus (T2D) presently ranks fourth among the diseases that result in human death worldwide. The latest data from the United Nations show that the number of diabetes mellitus patients worldwide has already reached 180 million. Moreover, T2D morbidity is rapidly increasing. To date, more than 20 million people in China have T2D [1]. However, the etiology and pathogenesis of T2D are yet to be completely clarified.

Type 2 diabetes mellitus is a common polygenic disorder with a complicated pathogenesis, a large number of complications, and high mortality rate. It is a chronic progressive disease characterized by impaired pancreatic β-cell function and insulin resistance (IR) [2]. Insulin resistance is one of the pathogenesis mechanisms for T2D [3,4]. Evidence shows that IR is inheritable

Author contributions: Conceived and designed the experiments: Li yan-yan. Performed the experiments: Li yan-yan. Analyzed the data: Li yan-yan. Contributed reagents/material/analysis tools: Li yan-yan.Wrote the manuscript: Li yan-yan. Reference collection and data management: Li yan-yan. Statistical analyses and paper writing: Li yan-yan.Study design: Li yan-yan.

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0026-0495/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2011.10.002

and attributable to several intrinsic factors. Insulin resistance can be detected in patients with insulin receptor gene mutation. However, cases of insulin receptor gene mutation in T2D patients are rare. Recently, a glycoprotein called *ectoenzyme nucleotide pyrophosphate phosphodiesterase 1* (*ENPP1*) was discovered to be highly expressed in the muscle, skin, and fat of T2D patients. *ENPP1* decreases the tyrosine protein phosphorylation level of the insulin receptor by combining with its α subunit. Thus, insulin signal transduction is hindered; and IR is induced [5]. Therefore, T2D gradually evolves.

ENPP1, a type II transmembrane glycoprotein, is located in the membrane serosa and endoplasmic reticulum. The possible mechanisms for the induction of IR by the *ENPP1* 121Q allele are as follows: (1) The autophosphorylation sites of serine and threonine in the tyrosine kinase activity region of the insulin receptor are altered, resulting in the blockage of the insulin information downstream cascade [6]. (2) The postreceptor signal transduction, independent of the tyrosine kinase activity, is blocked [7]. (3) *ENPP1* expression is consequently induced by the elevated serum insulin level through the rapid and sensitive signal mechanism [8].

The *ENPP1* gene located in 6q22-23 and spanning 80 kilobases contains 25 exons and 24 introns. The *ENPP1* K121Q gene polymorphism is located in the fourth exon and formed by a missense mutation in the 121st codon. The mutation of cytosine (C base), substituting for adenine (A base), in the 121st codon contributes to the replacement of lysine (K) by glutamine (Q) in the corresponding amino acid sequence.

Although *ENPP1* K121Q gene polymorphism is closely associated with T2D, relevant research results are still contradictory. In 2006, Grarup et al [9] assessed the effect of *ENPP1* K121Q polymorphism on T2D, obesity, and quantitative metabolic traits in 7333 Danes using meta-analysis. In the Danish meta-analysis, the *ENPP1* codon 121Q allele was found to be associated with T2D. In 2007, Meyre et al [10] detected nominal evidence of association between K121Q polymorphism and the risk of T2D in participants with a family history of T2D in pooled analyses. In 2008, McAteer et al [11] performed a meta-analysis including 42 042 subjects and found that the *ENPP1* 121Q variant increased the risk of T2D under a dominant model of inheritance in European populations. In 2009, El Achhab et al [12] reported an association between *ENPP1* 121Q and metabolic diseases in the Moroccan population. In 2010, Lee et al [13] also found that *ENPP1* K121Q polymorphism was associated with T2D and that the Q allele increased the incidence of aortic arch calcification in a Korean population.

In contrast, in 2006, Weedon et al [14] found that the *ENPP1* K121Q variant was not associated with T2D in 8089 white British subjects. In the same year, Lyon et al [15] found that the K121Q missense polymorphism was not significantly associated with T2D in individuals of European ancestry from the United States and Poland, as well as in African Americans. In 2009, Ezzidi et al [16] reported that no allelic or genotypic association with T2D was detected for *ENPP1* K121Q polymorphism in the Arabic population from Tunisia. In 2010, Bhatti et al [17] found that *ENPP1/PC-1* K121Q polymorphism was not associated with T2D and related quantitative metabolic traits in the North Indian Punjabi population in a case-control study. Analogously, in 2011, Saberi et al [18] found that the *ENPP1* 121Q allele might not be associated with T2D and related metabolic traits among Iranian subjects in another case-control study.

Several studies on the association between *ENPP1* K121Q gene polymorphism and T2D have been conducted in China, but the results are still controversial. In 2006, Chen et al [19] reported that *ENPP1* K121Q polymorphism was not related to T2D, to the features of the metabolic syndrome, or to the diabetic macrovascular complications in the Taiwanese population favored by other studies [1,20-23]. However, converse conclusions have been reached in other studies [24-31]. The present meta-analysis, which included 11 855 participants, was conducted to determine the relationship between *ENPP1* K121Q gene polymorphism and T2D in the Chinese population.

2. Materials and methods

2.1. Publication search and inclusion criteria

The medical subject headings *type 2 diabetes mellitus*, *polymorphism*, *ectoenzyme nucleotide pyrophosphate phosphodiesterase 1*, *gene*, and *Chinese* were used to retrieve related literature from electronic databases, such as PubMed, Embase, Web of Science, China Biological Medicine Database, and China National Knowledge Infrastructure. The publication year of the acquired studies ranged from 2002 to 2011 (last research updated on July 7, 2011).

The selected studies had to fulfill the following major criteria: (*a*) evaluation of *ENPP1* K121Q gene polymorphism and T2D in Chinese population and (*b*) diagnosis of T2D in accordance with the American Diabetes Association fasting plasma criteria (2005). The participants had either a fasting plasma glucose level of at least 7.0 mmol/L or a 2-hour plasma glucose result of at least 11.1 mmol/L via an oral glucose tolerance test.

2.2. Data extraction

The data were extracted following a standard protocol. In the present meta-analysis, repeated literature, studies deviating from the inclusion criteria, or those providing insufficient data were excluded. If similar data were obtained from different studies, the result was only adopted once. The drawn data contained the first author's name, the publication year, the region, the number of genotypes, the genotyping, the study design, the matching criteria, the total number of cases, and the controls.

2.3. Statistical analysis

The Q allele distribution frequency of the *ENPP1* K121Q, the KQ + QQ/KK values, and the QQ/KQ + KK values between the T2D and control groups were compared using the odds ratio (OR) corresponding to a 95% confidence interval (CI). A χ^2 test–based Q test was used to calculate the heterogeneity among the studies, and the significance was set at the $P < .10$ level [32]. The variation resulting from heterogeneity was assessed

Table 1 – Characteristics of the investigated studies of the association between *ENPP1* K121Q gene polymorphism and T2D in Chinese population

Author	Year	Region	Ethnicity	T2D			Control			Genotyping	Study design	Matching criteria	Sample size (T2D/control)
				KK	KQ	QQ	KK	KQ	QQ				
Du [24]	2002	Hubei	Han	146	65	6	40	12	2	PCR-RFLP	Case-control	Sex, ethnicity	217/54
Xu et al [25]	2003	Shandong	Han	77	30	0	83	9	0	PCR-RFLP	Case-control	Age, sex, ethnicity	107/92
Ren et al [26]	2004	Chongqing	Han	177	37	2	90	16	0	PCR-RFLP	Case-control	Sex, ethnicity	216/106
Yu et al [20]	2005	Shanghai	Han	143	22	0	85	12	1	PCR-RFLP	Case-control	Age, sex, ethnicity	165/98
Chen et al [19]	2006	Taiwan	Han	1515	333	14	681	155	8	PCR-RFLP	Case-control	ethnicity	1862/844
Liu [27]	2006	Shenzhen	Han	238	57	0	195	19	0	PCR-RFLP	Case-control	Age, sex, ethnicity	295/214
Lu [28]	2006	Liaoning	Han	92	26	1	361	59	2	PCR-RFLP	Case-control	Sex, ethnicity	119/422
Zhong et al [21]	2006	Shenzhen	Han	39	11	0	40	10	0	PCR-RFLP	Case-control	BMI, ethnicity	50/50
Chai et al [29]	2007	Shandong	Han	37	10	0	84	8	0	PCR-RFLP	Case-control	Sex, ethnicity	47/92
Li et al [30]	2008	Yunnan	Han	99	25	3	62	6	0	PCR-RFLP	Case-control	Sex, ethnicity	127/68
Wang et al [31]	2010	Hubei	Han	429	106	4	340	61	3	PCR-RFLP	Case-control	Sex, ethnicity	539/404
Zhang et al [1]	2010	Shandong	Han	89	11	0	131	19	0	PCR-RFLP	Case-control	Age, sex, ethnicity	100/150
Shi et al [22]	2011	Beijing	Han	508	123	8	701	178	6	PCR-RFLP	Case-control	ethnicity	639/885
Zhao et al [23]	2011	Shanghai	Han	1463	393	23	1610	385	19	PCR-RFLP	Case-control	ethnicity	1879/2014

PCR-RFLP indicates polymerase chain reaction–restriction fragment length polymorphism.

by calculating the inconsistency index I^2. If heterogeneity existed among the studies, the pooled OR was estimated using a random-effects model (the DerSimonian and Laird method) [33]. Otherwise, a fixed-effects model was used (the Mantel-Haenszel method) [34]. The pooled OR was determined using a Z test with significance set at $P < .05$.

The Hardy-Weinberg equilibrium was assessed using a Fisher exact test with significance set at $P < .05$. A funnel plot was used to assess potential publication bias. The funnel plot asymmetry was assessed using the linear regression test of Egger et al [35] on the natural logarithm scale (significance was set at the $P < .05$ level). The statistical analysis was performed using STATA 10.0 software (StataCorp, College Station, TX).

3. Results

3.1. *Studies and populations*

A total of 25 articles were acquired through the literature search, 14 of which complied with the inclusion criteria. Of the 11 excluded studies, 2 were repeated published literature, 1 was published in 2 different languages, 4 were reviews, and 4 were not associated with *ENPP1* K121Q gene polymorphism. No study was excluded for deviating from the Hardy-Weinberg equilibrium. The data were gathered from a total of 6362 T2D patients and 5493 controls (Table 1). The 9

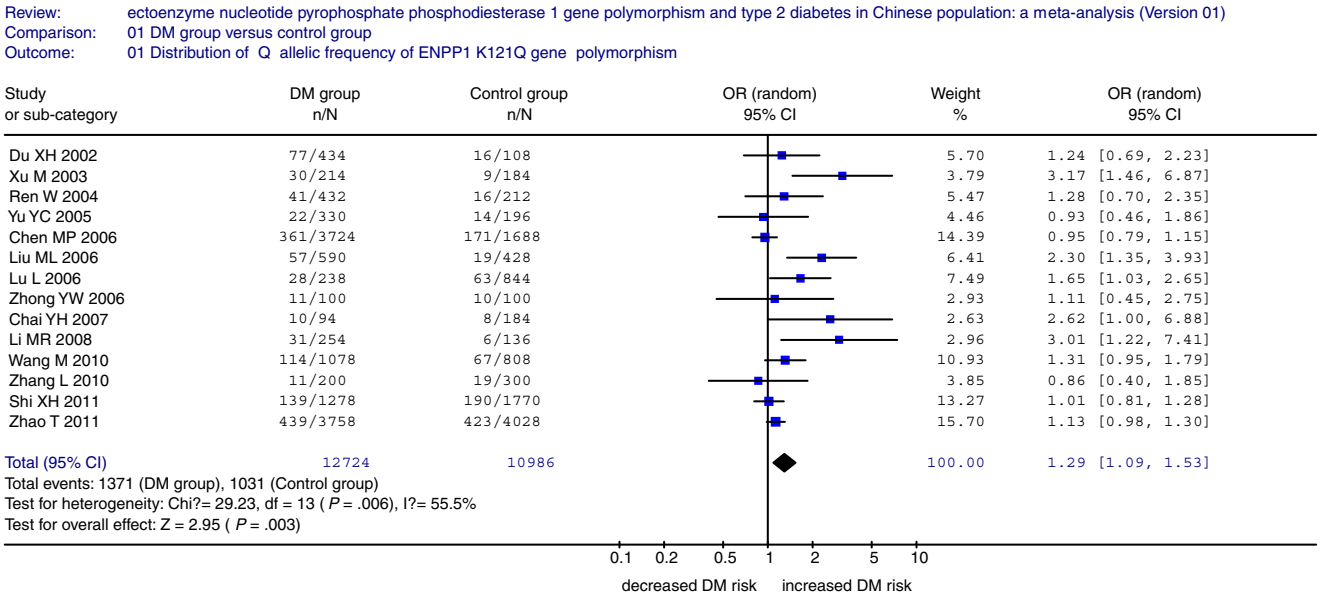

Fig. 1 – Forest plot of the allelic genetic model of T2D associated with K121Q gene polymorphism (distribution frequency of Q allelic of *ENPP1* K121Q gene).

Table 2 – Summary of meta-analysis of association of *ENPP1* K121Q gene polymorphism and T2D risk

	Pooled OR (95% CI)	Z (P)	I^2(%)
Distribution of Q allelic frequency	1.29 (1.09-1.53)	2.95 (P = .003)	55.5
KQ + QQ/KK	1.51 (1.20-1.91)	3.50 (P = .0005)	71.8
QQ/KQ + KK	1.20 (0.80-1.78)	0.87 (P = .38)	0

surveyed regions comprised the provinces of Hubei, Chongqing, Shanghai, Taiwan, Shenzhen, Liaoning, Yunnan, Beijing, and Shandong.

3.2. *Pooled analyses*

Under an allelic genetic model of inheritance, the distribution frequency of the Q allele was 0.107 for the T2D group and 0.093 for the control group. The pooled OR for the distribution of the Q allele frequency of the *ENPP1* K121Q gene was 1.29 (95% CI, 1.09-1.53; $P_{heterogeneity}$ = .006; I^2 = 55.5%). A significant association was found between *ENPP1* K121Q gene polymorphism and T2D in the Chinese population under an allelic model of inheritance (P = .003) (Fig. 1, Table 2).

Under a dominant model of inheritance, the KQ + QQ/KK value was 0.259 for the T2D group and 0.220 for the control group. The pooled OR for the KQ + QQ/KK value was 1.51 (95% CI, 1.20-1.91; $P_{heterogeneity}$ < .0001; I^2 = 71.8%). The association between *ENPP1* K121Q gene polymorphism and T2D in the Chinese population was significant under a dominant model of inheritance (P = .0005) (Fig. 2, Table 2).

Under a recessive model of inheritance, the QQ/KK + KQ value was 0.0097 for the T2D group and 0.0075 for the control group. The pooled OR for the QQ/KK + KQ value was 1.20 (95% CI, 0.80-1.78; $P_{heterogeneity}$ = .84; I^2 = 0). There was no significant association between *ENPP1* K121Q gene polymorphism and T2D in the Chinese population under a recessive model of inheritance (P = .38) (Fig. 3, Table 2).

Meta-regression was performed to explore the potential sources of heterogeneity under the dominant model of inheritance. The confounding factors included study regions, T2D group sample size, control group sample size, total sample size, ratio of T2D group sample size to control group sample size, T2D group mean body mass index (BMI), control group mean BMI, T2D group mean age, and control group mean age. However, only the mean age of the control group possibly explained the heterogeneity (P = .05). The other factors were not correlated with the heterogeneity (P > .10) (Tables 3 and 4).

In the subsection analysis stratified by the control group mean age, subsection 1 consisted of the studies with the control group mean age of at least 55 years. The studies with control group mean age less than 55 years were defined as subsection 2. In subsection 1 of 8 studies, the pooled OR for the KQ + QQ/KK value was 1.28 (95% CI, 1.02-1.60; $P_{heterogeneity}$ = .002; I^2 = 69.4%). In subsection 2 of 6 studies, the pooled OR for the KQ + QQ/KK value was 2.20 (95% CI, 1.30-3.74; $P_{heterogeneity}$ = .02; I^2 = 61.5%). Comparison of the T2D individuals with the controls revealed that the Q allele increased the T2D risk 0.28 times for subsection 1 and 1.20 times for subsection 2. The subsection analysis results indicated that the heterogeneity in subsection 1 was higher than that in subsection 2. The quality of the studies on subsection 1 required further improvement (Table 5, Fig. 4).

3.3. *Bias diagnostics*

A funnel plot and Egger test were used to assess the publication bias of the studies. No visual publication bias was found in the funnel plot (Fig. 5). The difference in the

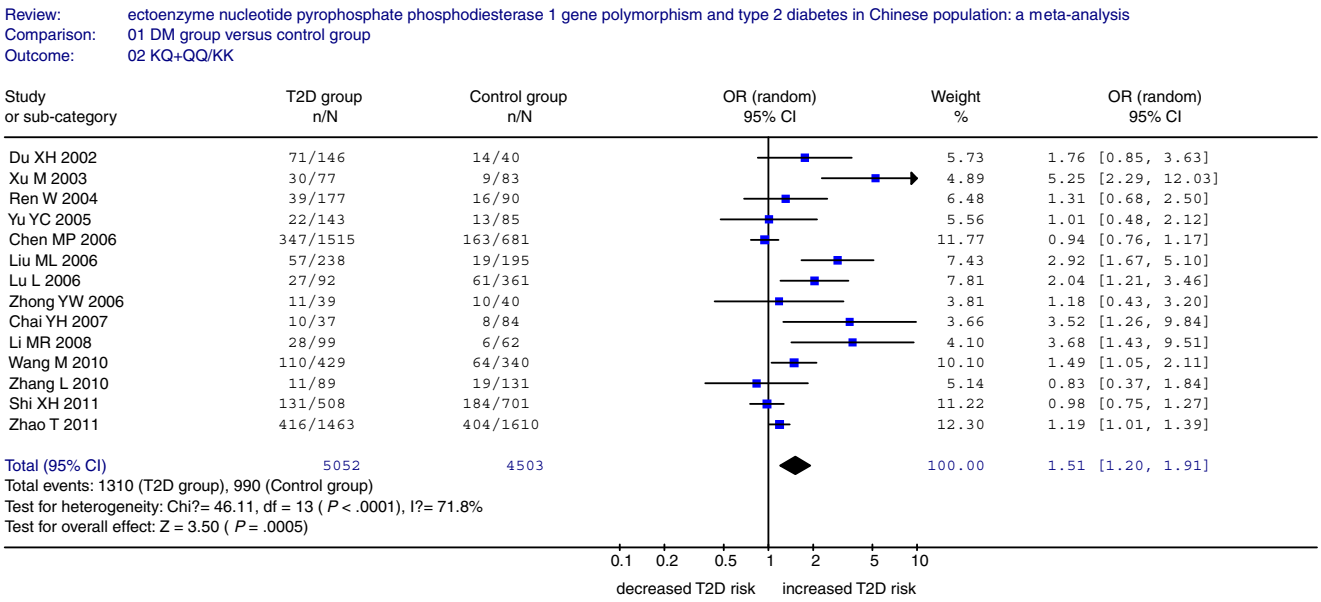

Fig. 2 – Forest plot of the dominant genetic model of T2D associated with K121Q gene polymorphism (KQ + QQ/KK value of *ENPP1* K121Q gene).

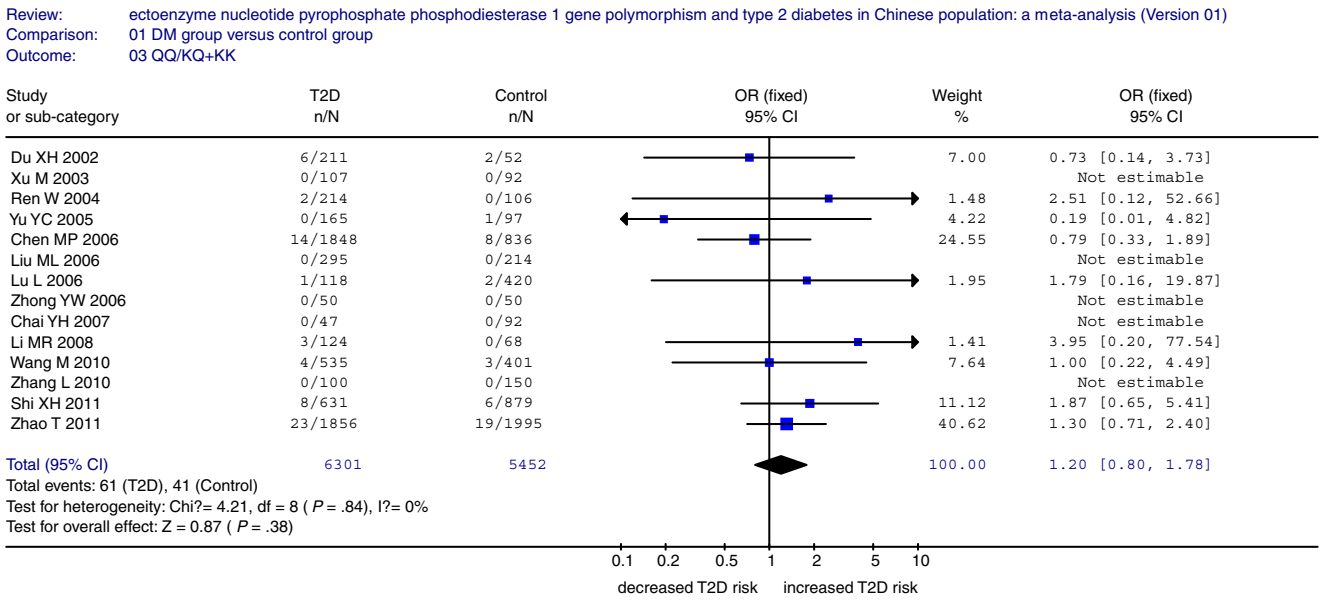

Fig. 3 – Forest plot of the recessive genetic model of T2D associated with K121Q gene polymorphism (QQ/KK + KQ value of *ENPP1* K121Q gene).

Egger test was not statistically significant, which implies low publication bias in the present meta-analysis ($P > .05$).

4. Discussion

In the present study on 11 855 Chinese subjects, *ENPP1* K121Q gene polymorphism was shown to be associated with T2D susceptibility using an allelic genetic model and a dominant genetic model. No significant association was found between them using a recessive genetic model that was probably associated with the QQ genotype number. There was no QQ genotype in 5 studies, and the corresponding OR could not be estimated.

In the past years, much effort has been done and a great deal of controversy surrounded the relationship between *ENPP1* K121Q gene polymorphism and T2D risk. Some studies have detected nominal evidence of the association between K121Q polymorphism and the risk of T2D [9-13,36-38]. The results of other studies were contradictory [14-18]. In the current meta-analysis, the association of the variation in *ENPP1* with T2D was successfully replicated. People with the Q allele of the *ENPP1* K121Q gene might be at high risk for T2D. The primary result of the current research was consistent with the meta-analysis results in the European population study performed by McAteer et al [11].

In the following meta-regression, the confounding factor, the mean age of the control group, was considered as the

Table 3 – The confounding factors for the potential sources of heterogeneity studied by meta-regression

Study	Year	Region	Case size	Control size	Total size	RR	Case BMI	Control BMI	Case age	Control age	LnOR
Du [24]	2002	1	217	54	271	4.02	25.55 ± 3.22	23.23 ± 3.19	50.80 ± 9.80	43.40 ± 10.70	0.57
Xu et al [25]	2003	2	107	92	199	1.16	25.80 ± 2.80	24.00 ± 1.10	56.40 ± 11.90	50.3 ± 10.4	1.66
Ren et al 26]	2004	1	216	106	322	2.04	24.00 ± 3.00	24.00 ± 3.00	52.00 ± 12.00	45.00 ± 13.00	0.27
Yu et al [20]	2005	1	165	98	263	1.68	25.21 ± 4.28	24.42 ± 4.17	55.56 ± 10.65	53.81 ± 15.17	0.01
Chen et al [19]	2006	1	1862	844	2706	2.21	25.40 ± 3.60	24.00 ± 3.30	62.20 ± 12.10	64.50 ± 9.50	−0.06
Liu [27]	2006	1	295	214	509	1.38	23.38 ± 3.40	22.78 ± 3.00	58.27 ± 13.49	55.92 ± 11.01	1.07
Lu [28]	2006	2	119	422	541	0.28	25.60 ± 3.14	23.47 ± 3.21	58.00 ± 11.30	55.00 ± 10.40	0.71
Zhong et al [21]	2006	1	50	50	100	1.00	23.15 ± 3.35	23.46 ± 2.17	58.74 ± 14.06	55.73 ± 8.50	0.17
Chai et al [29]	2007	2	47	92	139	0.51	25.21 ± 3.47	23.48 ± 3.51	56.40 ± 11.90	50.34 ± 10.40	1.26
Li et al [30]	2008	1	127	68	195	1.87	24.82 ± 3.26	23.17 ± 3.19	55.80 ± 14.29	44.15 ± 9.17	1.3
Wang et al [31]	2010	1	539	404	943	1.33	24.19 ± 4.39	22.07 ± 4.26	55.46 ± 12.79	61.10 ± 12.67	0.4
Zhang et al [1]	2010	2	100	150	250	0.67	25.50 ± 3.35	22.31 ± 3.11	56.40 ± 12.1	55.20 ± 15.1	−0.19
Shi et al [22]	2011	2	639	885	1524	0.72	25.05 ± 3.60	24.16 ± 3.15	69.20 ± 6.30	67.80 ± 5.69	−0.02
Zhao et al [23]	2011	1	1879	2014	3893	0.93	25.30 ± 3.40	24.50 ± 3.20	63.80 ± 9.00	58.10 ± 9.00	0.17

Region 1: southern China; region 2: northern China. RR indicates the ratio of case size to control size; LnOR, the natural logarithm of OR for KQ + QQ/KK between T2D and control groups.

Table 4 – The meta-regression results among 14 studies

Item	Coefficient	Standard error	*T* value	*P* value	95% CI
Publication year	−0.13966	0.0804307	−1.74	.12	−0.3251335 to −0.0458134
Ratio of T2D and control group size	−0.2392199	0.1801896	−1.33	.22	−0.6547378 to 0.1762979
Control BMI	−0.4309148	0.268203	−1.61	.15	−1.049392 to 0.1875624
T2D group age	0.1270666	0.0767293	1.66	.14	−0.0498716 to 0.3040047
Control group age	−0.0855189	0.0372846	−2.29	0.05 *	−0.1714973 to 0.0004595
Summation	288.554	162.8144	1.77	.114	−86.89659 to 664.0046

* $P < .10$

source of heterogeneity. The control group mean age could explain the heterogeneity, which suggested that the non-uniformity in the mean age of the control subjects contributed to the heterogeneity among the individual studies. The effect of genetics was greater in studies involving younger control subjects. After adjusting for the age of the control group, unexplained heterogeneity was still present. The association of the QQ genotype with T2D was evidently weakened, but still significant. K121Q might be mediated by its effects on age. If the *ENPP1* K121Q gene polymorphism contributed to T2D based on age, studies that exaggerated the age difference between the T2D and control participants (eg, by lowering the mean age of the control group) might have more easily obtained significant associations. Hence, further studies have to match the age between the cases and the controls.

This source of heterogeneity was different from that of McAteer et al [11], who also performed a meta-regression analysis and found that the mean BMI of the control subjects partially explained the observed heterogeneity. However, in the current meta-regression, BMI was unrelated to the heterogeneity ($P > .10$). This unrelated result was possibly associated with the moderate body type of the Chinese population. The difference in BMI between T2D and the control in Chinese population was probably not as great as that in European populations. In addition, 11 855 participants composed of 6362 T2D patients and 5493 controls were included in our study. However, in the study by McAteer et al, 42 042 subjects with 15 801 cases and 26 241 controls were involved. The total sample size of the current meta-analysis was much smaller than that of McAteer et al, which might also contribute to the difference in the source of heterogeneity.

Table 5 – Subsection analysis summary of the dominant genetic model by control group age (KQ + QQ/KK)

Subsection by control group age	Literature no.	Weight (%)	Pooled OR (95% CI)	*Z* (*P*)	I^2 (%)
Subsection 1: age ≥55 y	8	69.57	1.28 (1.02-1.60)	2.13 (*P* = .03)	69.4
Subsection 2: age <55 y	6	30.43	2.20 (1.30-3.74)	2.92 (*P* = .004)	61.5
Whole population	14	100.0	1.51 (1.20-1.91)	3.50 (*P* = .0005)	71.8

Limitations in the present research inevitably exist, and these include following points: (1) In the present meta-analysis, the eventual analysis results were possibly influenced by the different subjects control conditions. For example, the different matching criteria for control and T2D groups among the studies contributed to the heterogeneity. Sex and ethnicity were regarded as the matching criteria in 6 studies. Otherwise, age was also looked upon as the matching criterion in 4 studies. Furthermore, ethnicity alone was adopted as the matching criterion in 3 studies. Besides, BMI was used as the matching criterion only in one study. (2) Larger sample sizes are needed in future studies to exclude the interference factors of genetic risk contributed by the Q variants of modest effects, especially when they played their role via a recessive model. In the current meta-analysis, there were just 6 studies with the sample size greater than 500. Moreover, the sample size was merely 100 in an individual study. (3) Other gene polymorphisms should be examined comprehensively to explore the virtual role of *ENPP1* K121Q gene polymorphism in T2D. For instance, the transcription factor 7-like 2 (*TCF7L2*) rs7903146 TC gene polymorphism was also associated with the increased T2D risk [39,40].

In summary, the current meta-analysis indicated that, in the Chinese population, the Q allele of the *ENPP1* K121Q gene polymorphism might increase T2D risk and that Q allele carriers are predisposed to T2D. The interaction between genotype and age might partially explain the residual heterogeneity. In consideration of the aforementioned limitations, the conclusion has to be verified through further studies in China.

Funding

None.

Acknowledgment

We thank all our colleagues working in the Department of Geriatrics, the First Affiliated Hospital of Nanjing Medical University.

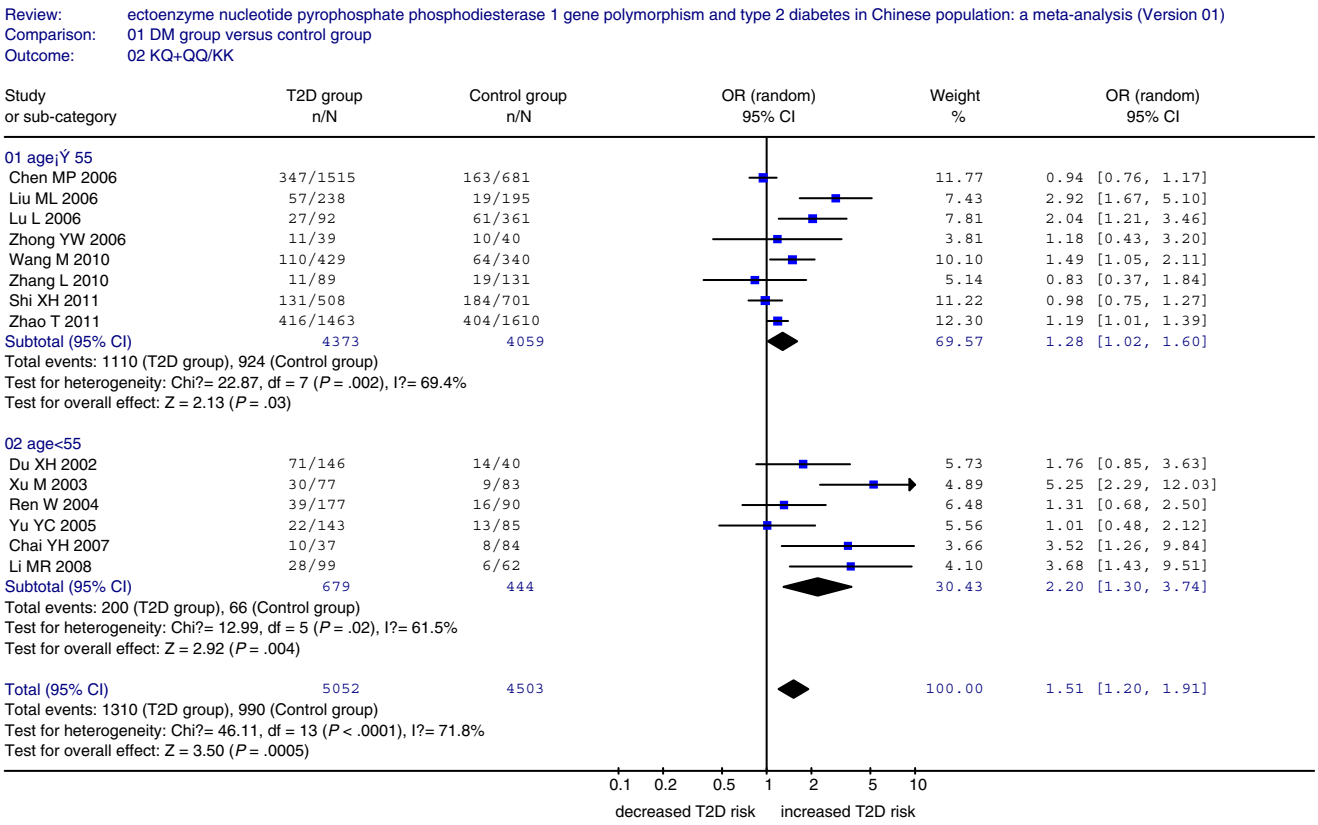

Fig. 4 – Forest plot of the dominant genetic model of T2D associated with K121Q gene polymorphism stratified by control group mean age (KQ + QQ/KK value of *ENPP1* K121Q gene).

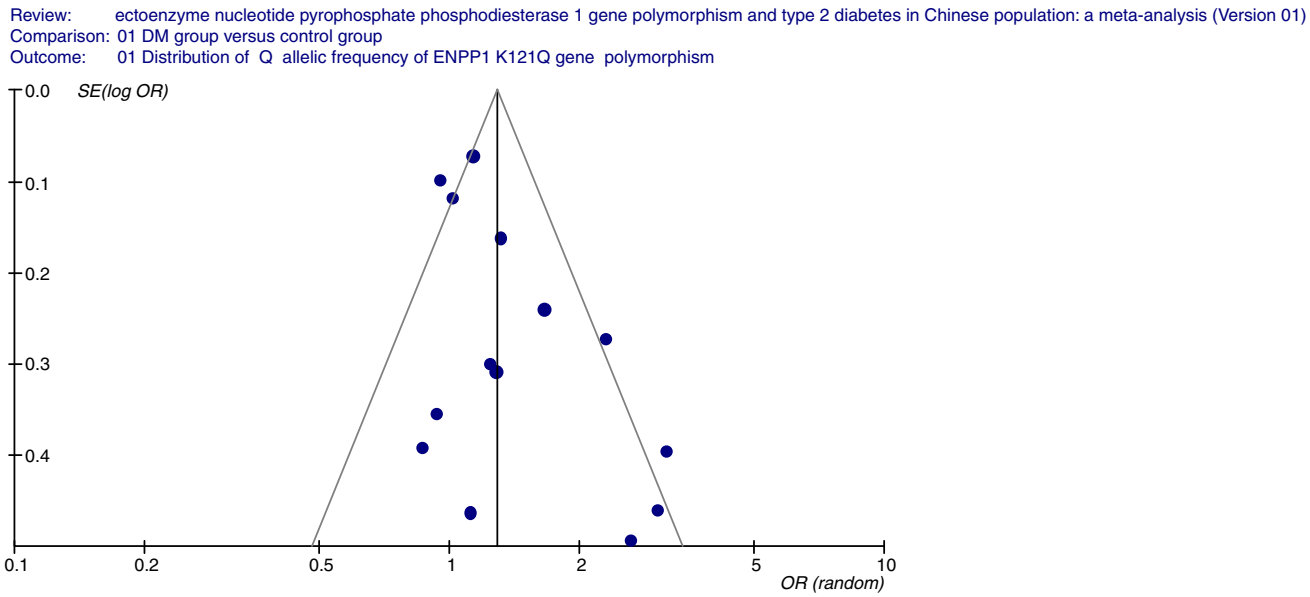

Fig. 5 – Funnel plot for studies of the association of T2D and *ENPP1* gene polymorphism (distribution frequency of Q allelic of *ENPP1* 1 K121Q gene). The horizontal and vertical axes correspond to the OR and confidence limits. SE indicates standard error.

Conflict of Interest

None.

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