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Original Article

Ectonucleotide pyrophosphatase/phosphodiesterase 1 (K121Q rs1044498) polymorphism is associated with diabetic nephropathy but not obesity among type-2 diabetes mellitus Egyptian patients

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Abstract

Introduction

Genetics contribute to the development of type-2 diabetes mellitus (T2DM), its complications, and phenotypes such as diabetic nephropathy (DN) and obesity. Although the likely associations among the ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) gene, DN and obesity have been massively investigated, the results are still controversial. This study aimed to assess whether *ENPP1* K121Q (A/C rs1044498) variant is associated with DN and obesity in T2DM Egyptian patients. We genotyped this variant in a total of 183 T2DM Egyptian patients who were classified into cases (91 participants with moderately increased albuminuria or severely increased albuminuria ≥ 30 mg/g) and controls (92 patients with normoalbuminuria <30 mg/g) using TaqMan technology.

Results

Patients, with the C (minor/risk) allele, had significantly higher moderately increased albuminuria/severely increased albuminuria levels ($P < 0.001$) and albumin-to-creatinine ratio ($P = 0.001$) than those with the wild A allele. AC and CC genotypes of *ENPP1* K121Q (A/C, rs1044498) variant and its C-allele frequencies are significantly higher in cases than controls ($P = 0.043$ and 0.013), respectively, and in patients with estimated glomerular-filtration rate (eGFR) less than 60 than those with eGFR more than 60 ($P = 0.014$ and 0.004), respectively. AC and CC genotypes are associated with cases with a significant odds ratio in both dominant [odds ratio (OR): 2.003, 95% confidence interval (CI): 1.106–3.628, $P = 0.022$) and additive (OR: 1.865, 95% CI: 1.134–3.070, $P = 0.014$) models of inheritance and in patients with eGFR less than 60 in the dominant model of inheritance (OR: 2.398, 95% CI: 1.258–4.571, $P = 0.008$), but showed no association with obesity ($P > 0.05$).

Conclusion

ENPP1 K121Q (A/C, rs1044498) variant is associated with DN but not obesity among Egyptian T2DM patients.

Keywords: Diabetic nephropathy, ectonucleotide pyrophosphatase/phosphodiesterase 1 K121Q rs1044498 variant, obesity, type-2 diabetes mellitus

Introduction

Type-2 diabetes mellitus (T2DM) is a chronic multifactorial disorder that affects glucose homeostasis, leading to chronic hyperglycemia. It accounts for more than 90% of the cases of diabetes in adults [1]. In 2019, Egypt was ranked as the ninth leading country in the world for the number of patients with T2DM (8.9 million). This ranking will progress to the eighth in 2030 (11.9 million) and the seventh in 2045 (16.9 million) [2].

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It has been estimated that 20–40% of those with T2DM will develop diabetic nephropathy (DN) [3] with ~13-fold higher risk of end-stage renal disease (ESRD) [4]. This common and most serious microvascular complication of T2DM [5] is detected and monitored by persistent high urinary albumin excretion more than or equal to 30 mg/g and/or sustained reduction in estimated glomerular-filtration rate (eGFR) less than 60 ml/min/1.73 m^2 [6], together with elevated serum urea and creatinine levels [7]. The United Kingdom Prospective Diabetes Study (UKPDS) revealed that annually 2.8% of T2DM patients showed progression from moderately increased albuminuria formerly known as microalbuminuria (uAlb) to severely increased albuminuria formerly known as macroalbuminuria (Malb) and 2.3% progressed to ESRD [8]. DN develops due to multiple interacting mechanisms such as hyperglycemia that implicates metabolic and hemodynamic alterations associated with hyperfiltration and genetic predisposition [9]. These mechanisms result in basement-membrane thickening, mesangial expansion, nodular glomerulosclerosis with classic Kimmelstein–Wilson nodules, and development of fibrosis [10]. The prevalence of uAlb and Malb among T2DM Egyptian patients was 34.2 and 12.8%, respectively, in one study [11] and 31.8 and 7.9%, respectively, in another study. These findings provide a clue of the prevalence of DN in Egypt, in addition to 36.4% who were in high risk according to the eGFR [12]. The pattern of initiation of DN and the development of ESRD in different ethnic groups, together with the familial aggregation, suggest a contribution of genetic factors [13]. This is reinforced by the fact that only a certain percentage of T2DM patients develop DN and progress to ESRD although they are all exposed to the same environmental factors [14]. Also, obesity (BMI ≥30 kg/m^2) has a marked correlation with T2DM [15] and both show a cause-and-effect interrelationship. Not only people who are genetically predisposed to develop T2DM are prone to become obese because of insulin resistance (IR), but this resistance triggers increased hepatic glucose production and insulin release that in turn are the cause of obesity [16]. It is worthy to note that the prevalence of obesity among Egyptian adults is 32.0% (27.6–36.6) [17].

Genetics play an important role in the development of diabetes [1]. Ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) K121Q (A/C, rs1044498) variant has been associated with T2DM in the Egyptian population [18]. *ENPP1* gene, which is located on the long arm of chromosome 6 (6q22–23), is a transmembrane glycoprotein that determines the insulin sensitivity by encoding for a protein that inhibits the signaling of the insulin receptor [19]. A common missense single-nucleotide polymorphism (SNP), K121Q (A/C, rs1044498), in exon 4 of the *ENPP1* gene results in the substitution of the amino acid lysine (K) to glutamine (Q) in codon 121 (Q allele corresponds to the C allele) [20], which increases its inhibitory power and in turn blocks the tyrosine kinase activity of the insulin receptor in several cells, causing IR [21]. Some studies hypothesized its potential association with various parameters, including DN [22–24] and obesity [25,26] in T2DM patients of different ethnic groups and that the variant-allele frequency may be strongly linked to racial descent [27]. In accordance with these studies, we aimed to assess whether the *ENPP1* K121Q (A/C, rs1044498) variant is associated with DN and obesity in Egyptian patients with T2DM.

Patients and methods

A total of 183 T2DM patients aged 35–70 years old were recruited from the inpatient and outpatient clinics of the Internal Medicine Department of the National Institute of Diabetes and Endocrinology (NIDE) during the period from 2019 to 2020. Signed informed consent was taken from every recruited patient, after the approval of the research ethics committee of the General Organization of Teaching Hospitals and Institutes (GOTHI). All the enrolled patients (50 males and 133 females) were previously diagnosed as T2DM according to the criteria of the American Diabetes Association (ADA) in 2020 [28].

According to the guidelines of the ADA in 2020 [29], these patients were divided into two groups:

(1) Cases: 91 patients with uAlb or Malb more than or equal to 30 mg/g.
(2) Controls: 92 patients with normoalbuminuria less than 30 mg/g.

Exclusion criteria included patients less than 18 years with no previous history of a chronic kidney disease (CKD). All patients were subjected to history taking and full clinical examination. The participants' various parameters, including age, sex, duration of diabetes, height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP), were recorded. Height and weight were used to calculate BMI using adult BMI calculator (kg/m^2). Obesity was defined as individuals with BMI more than or equal to 30 kg/m^2 [30] and hypertension was defined as SBP more than or equal to 130 mmHg and/or DBP more than or equal to 85 mmHg or if the patients were taking any antihypertensive medications [31].

Sampling and biochemical analysis

After an overnight (12 h), with no caloric intake, two samples of blood were collected on EDTA-coated vacutainers: the first was refrigerated at −20°C, until used for extraction of DNA and the second was used for the estimation of glycated hemoglobin by D-10 high-performance liquid chromatography ion-exchange chromatography (Bio-Rad, Hercules, California, USA). Another blood sample was collected in serum-separation tubes for measuring fasting blood glucose, kidney-function tests (creatinine and urea), and lipid profile (cholesterol, triglycerides, high-density lipoprotein-density cholesterol, and low-density lipoprotein cholesterol) by conventional methods. Random spot-urine samples were collected in sterile containers to measure albumin and creatinine. Albumin was analyzed using immunoturbidimetric method and creatinine was assayed using enzymatic (creatininase)

method. All biochemical serum and urinary analyses were done using Cobas 8000 modular analyzer series (Roche Diagnostics, Indianapolis, Indiana, USA). Urinary albumin : creatinine ratio (ACR) was calculated by dividing albumin in mg/dl/creatinine in g/dl (normal ACR <30 mg/g) [32]. Exclusion criteria for the urine samples included blood in the urine, recent vigorous exercise, urinary-tract infection, fever, and sustained upright posture as these tend to increase albumin-excretion rates. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation method was used to calculate eGFR [33]. We considered the threshold value of eGFR less than 60 ml/min/1.73 m^2, which was used to make the diagnosis of CKD, to be abnormal [34].

DNA genotyping

DNA was extracted from 200 µl of frozen whole blood containing EDTA anticoagulant using the Qiagen Extract kit (Qiagen, Hilden, Germany) and following the manufacturer's instructions. The purity and concentration of the extracted DNA in an elution volume of 200 µl was determined by using Nano-Drop ND-1000 spectrophotometer measurement of absorbance at 260 and 280 nm (Thermo Fisher Scientific, Waltham, Massachusetts, USA) and then was stored at −80°C. We used Applied Biosystems (Applied Biosystems, Foster City, California, USA) allele-specific designed fluorescent TaqMan probes and designed primers with the ABI 7500 real-time PCR system platform for *ENPP1* K121Q (A/C, rs1044498) SNP genotyping. The forward primer was 5′-CTGTGTTCACTTTGGACATGTTG-3′ and the reverse primer was 5′-GACGTTGGAAGATACCAGGTTG-3′. These primers were selected similar to previous studies done for the *ENPP1* K121Q (A/C, rs1044498) SNP [22,35]. Standard PCR was performed using TaqMan Universal PCR Master Mix reagent kits according to the provided guidelines. The utilized thermal cycle included heating at 95°C (10 min) for initial denaturation (this step denatured the initial template into single-stranded DNA and also activated hot-started polymerases), followed by 40–50 cycles at 95°C (15 s) for denaturation, 60–62°C (1 min) for annealing of the primers to the template, 72°C (40 s) for primer extension, and finally 72°C (5 min) for final extension (post-PCR step that allows reannealing of the PCR yield into double-stranded DNA). The duplicate samples showed more than 95% of genotyping success, with a calculated error rate based on PCR duplicates of less than 0.01%. The genotyping was processed according to the manufacturer's protocol at the facility of Clinilab laboratories (Clinilab, Maadi, Cairo, Egypt).

Statistical analysis

Statistical data were analyzed by SPSS, version 13 for Windows (SPSS Inc., Chicago, Illinois, USA). Quantitative data were reported in terms of mean ± SD. Comparative statistical analysis was carried out using Student's *t* test or one-way analysis of variance as appropriate. Categorical data association was done using χ^2 test for independence (Fisher's exact test was used when cells have frequencies lower than 5). Binary logistic regression was used for study of genetic models and to determine odds ratios for subgroups of categorical variables. A *P* value less than 0.05 was considered significant. χ^2 goodness-of-fit test was performed in our study to confirm that the genotypic distribution of *ENPP1* variant did not deviate from the Hardy–Weinberg equilibrium ($P > 0.05$).

Results

This case–control study included 183 T2DM patients. In Table 1, all participants recruited in the study were classified according to *ENPP1* K121Q (A/C, rs1044498) variant genotypes, provided that A is the wild/major allele and C is the risk/minor allele. The AA (reference) genotype frequency is 56.8% ($n = 104/183$), while that of the combined AC + CC genotypes is 43.2% ($n = 79/183$). Demographic and biochemical features of the two genotype groups show that patients with the AC + CC genotypes have significantly higher uAlb/Malb levels and ACR than those with the homozygous AA genotype (505 ± 128 vs. 172 ± 29 mg/g, $P < 0.001$) (345 ± 43 vs. 175 ± 26 mg/g, $P = 0.001$), respectively. No other variables show any significant difference between the two genotype groups.

Table 2 represents demographic and biochemical characteristics of the cases ($n = 91$) (42 with uAlb + 49 with Malb) and the controls ($n = 92$ with normoalbuminuria). The cases have statistically significant higher cholesterol, high-density lipoprotein-density cholesterol, low-density lipoprotein cholesterol, urea, creatinine, uAlb, and ACR and lower

Table 1: Demographic and laboratory characteristics according to the ectonucleotide pyrophosphatase/phosphodiesterase 1 variant genotypes (AA vs. AC + CC)

Parameters	AA (*n*=104) (56.8%)	AC + CC (*n*=79) (43.2%)	*P*
Age (years)	50±1.0	50±1.3	0.778
Duration (years)	10±0.7	10.7±0.7	0.733
BMI (kg/m^2)	31.4±0.4	29.8±0.5	0.069
SBP (mmHg)	130.8±1.2	131±1.5	0.608
DBP (mmHg)	81.6±0.7	82.4±0.9	0.535
FBG (mg/dl)	172.3±5.9	178.5±6.7	0.492
A1c (%)	8.3±0.1	8.4±0.1	0.739
Chol (mg/dl)	212.6±4.1	215.9±5.7	0.402
TG (mg/dl)	169.8±8.1	165.4±10.1	0.099
HDL-c (mg/dl)	42.2±0.9	42.5±1.2	0.418
LDL-c (mg/dl)	133.2±4.1	139.2±4.9	0.150
Urea (mg/dl)	39.6±2.5	45.8±3.6	0.364
Creat (mg/dl)	1.1±0.1	1.3±0.1	0.139
uAlb (mg/g)	172±29	505±128	<0.001*
ACR (mg/gm)	175±26	345±43	0.001*
eGFR (ml/min/1.73 m^2)	73±2	69±3	0.054

Values are expressed as mean±SD. A1c, glycated hemoglobin; ACR, albumin-to-creatinine ratio; Chol, cholesterol; Creat, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular-filtration rate; FBG, fasting blood glucose; HDL-c, high-density lipoprotein-density cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; uAlb, moderately increased albuminuria. **P* value less than 0.05 (significant).

eGFR ($P < 0.05$) when compared with the controls. No significant differences were found between the two groups as regards sex, age, duration of diabetes, SBP, DBP, fasting blood glucose, glycated hemoglobin, triglycerides, and BMI ($P > 0.05$).

Table 3 shows the genotypic and allelic frequencies of *ENPP1* K121Q (rs1044498) variant among cases and controls. AC and CC genotypes are significantly higher among the cases $n = 39$ (42.9%) and $n = 8$ (8.8%), respectively, than in the controls $n = 29$ (31.5%) and $n = 3$ (3.3%), respectively ($P = 0.043$). The same finding applies for the minor allele C that is also higher in the cases $n = 55$ (30%) than the controls $n = 35$ (19%) ($P = 0.013$). Table 3 also represents the odds-ratio analysis, showing that the carriers of C allele of the *ENPP1* K121Q (rs1044498) in the patients with AC and CC genotypes have a higher prevalence of uAlb/Malb about two times as much than in patients with AA genotype under dominant AC + CC versus AA [odds ratio (OR): 2.003, 95% confidence interval (CI): 1.106–3.628, $P = 0.022$] and about 1.9 times as much under additive CC versus AC versus AA (OR: 1.865, 95% CI: 1.134–3.070, $P = 0.014$) models of inheritance.

Table 2: Demographic and laboratory characteristics of cases and controls

Parameters	Cases uAlb/ Malb ≥30 mg/g (n=91)	Controls Nalb <30 mg/g (n=92)	P
Age (years)	51±1	50±1.1	0.335
Duration (years)	10.4±0.6	10.2±0.8	0.814
BMI (kg/m^2)	30.9±0.4	30.4±0.5	0.477
SBP (mmHg)	131.6±1.2	129.2±1.4	0.212
DBP (mmHg)	82.8±0.8	81.2±0.9	0.174
FBG (mg/dl)	181.1±3.3	169.0±8.2	0.176
A1c (%)	8.5±0.	8.1±0.2	0.081
Chol (mg/dl)	225.6±5.4	202.6±3.7	<0.001*
TG (mg/dl)	165±9.1	170.7±8.9	0.656
HDL-c (mg/dl)	43.9±1.1	40.7±0.9	0.023*
LDL-c (mg/dl)	146±5.2	125.6±3.3	0.001*
Urea (mg/dl)	53.1±3.9	31.5±0.8	<0.001*
Creat (mg/dl)	1.4±0.1	1.0±0.1	<0.001*
uAlb (mg/g)	505.6±44.4	13.5±0.6	<0.001*
ACR (mg/g)	484.1±36	15.5±0.6	<0.001*
eGFR (ml/min/1.73 m^2)	62.8±3	80.1±2	<0.001*

Values are expressed as mean±SD. A1c, glycated hemoglobin; ACR, albumin-to-creatinine ratio; Chol, cholesterol; Creat, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular-filtration rate; FBG, fasting blood glucose; HDL-c, high-density lipoprotein-density cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; uAlb, moderately increased albuminuria. *P value less than 0.05 (significant).

Table 4 shows the genotypic and allelic frequencies of *ENPP1* K121Q (rs1044498) variant among patients with eGFR less than 60 ($n = 55$) and those with eGFR more than 60 ($n = 128$). AC and CC genotypes are significantly higher among those with eGFR less than 60 $n = 26$ (47%) and $n = 6$ (11%), respectively, than those with eGFR more than 60 $n = 42$ (33%) and $n = 5$ (4%), respectively (P 0.014). Also, the same finding applies for the minor allele C that is higher in the patients with eGFR less than 60 $n = 38$ (34%) than those with eGFR more than 60 $n = 52$ (20%) ($P = 0.004$). The odds-ratio analysis showed that the patients with eGFR less than 60 were more prevalent (2.398 times) in the CC + AC group than in the AA group as explained by the dominant genetic model of inheritance (OR: 2.398, 95% CI: 1.258–4.571, $P = 0.008$).

The genotypic and allelic frequencies of *ENPP1* K121Q (rs1044498) show no statistically significant difference as regards obesity (BMI ≥30 and BMI <30) ($P > 0.05$) (Table 5).

Discussion

The prevalence of T2DM is rapidly increasing in Egypt according to the information provided by the International Diabetes Federation (IDF) [2]. DN is considered the most common cause of CKD all over the world and may end with kidney failure [36]. Almost 25–40% of all T2DM patients will likely develop DN [29]. However, it is not clear why DN progression occurs only in some and not all T2DM patients. Studies stated that both familial clustering and SNP heritability had a role in its development, supporting a genetic contribution

Table 3: Comparison between cases and controls as regards ectonucleotide pyrophosphatase/phosphodiesterase 1 genotype distribution and allele frequency in different inheritance models

Genotypes and alleles	Cases (n=91) uAlb + Malb ≥30 mg/g	Controls (n=92) Nalb <30 mg/g	P
AA genotype	44 (48.4)	60 (65.2)	0.043*
AC genotype	39 (42.9)	29 (31.5)	
CC genotype	8 (8.8)	3 (3.3)	
A allele	127 (70)	149 (81)	0.013*
C allele	55 (30)	35 (19)	
Genetic model	**OR**	**95% CI**	**P**
Dominant (AC + CC vs. AA)	2.003	1.106-3.628	0.022*
Recessive (CC vs. AC + AA)	2.859	0.734-11.43	0.130
Additive (CC vs. AC vs. AA)	1.865	1.134-3.070	0.014*
C allele	1.844	1.135-2.996	0.013*

Data are reported as absolute frequency (percentage of the respective patient group). CI, 95% confidence interval; Malb, severely increased albuminuria; Nalb, normoalbuminuria; OR, odds ratio; uAlb, moderately increased albuminuria. *P value less than 0.05 (significant).

Table 4: Comparison between patients with estimated glomerular-filtration rate less than 60 and more than 60 as regards ectonucleotide pyrophosphatase/ phosphodiesterase 1 genotype distribution and allele frequency in different inheritance models

Genotypes and alleles	eGFR <60 (*n*=55)	eGFR >60 (*n*=128)	*P*
AA genotype	23 (42)	81 (63)	0.014*
AC genotype	26 (47)	42 (33)	
CC genotype	6 (11)	5 (4)	
A allele	72 (66)	204 (80)	0.004*
C allele	38 (34)	52 (20)	
Genetic model	**OR**	**95% CI**	***P***
Dominant (AC + CC vs. AA)	2.398	1.258-4.571	0.008*
Recessive (CC vs. AC + AA)	3.012	0.879-10.328	0.079
Additive (CC vs. AC vs. AA)	0.892	0.533-1.491	0.662
C allele	2.071	1.259-3.404	0.004*

Data reported as absolute frequency (percentage of the respective patient group). CI, 95% confidence interval; eGFR, estimated glomerular-filtration rate; OR, odds ratio. **P* value less than 0.05 (significant).

Table 5: Comparison between the studied patients according to BMI more than or equal to 30 and less than 30 as regards ectonucleotide pyrophosphatase/ phosphodiesterase 1 genotype distribution and allele frequency in different inheritance models

Genotypes and alleles	BMI ≥30 (*n*=90)	BMI <30 (*n*=93)	*P*
AA genotype	57 (63.3)	47 (50.5)	0.198
AC genotype	29 (32.2)	39 (41.9)	
CC genotype	4 (4.4)	7 (7.5)	
A allele	143 (79.4)	133 (71.5)	0.077
C allele	37 (20.6)	53 (28.5)	

Data reported as absolute frequency (percentage of the respective patient group). *P* value less than 0.05 (significant).

according to the ethnic group [37,38]. Also, obesity that is a pronounced feature of the typical phenotype of the patients with T2DM [39], is estimated to be an independent predictor of kidney complications in patients with T2DM [40].

Common genetic risk variants for T2DM, DN, and obesity are present both within and between populations. The genetic architecture shows the possible role of these risk variants' effects, in differences in risk, among the variable populations and ethnic groups [41].

The aim of this case–control study is to assess the association of *ENPP1* K121Q (rs1044498) variant with both DN and obesity among adult Egyptian T2DM patients as it has been extensively investigated in association with T2DM, its various phenotypes, and complications in other different populations. We were encouraged to reveal this association among Egyptian T2DM patients as there were conflicting results, based on different studies related to the different populations, as regards the aforementioned phenotype and complication. These contradictory results, depending on the stated finding that the C- (risk) allele frequency varies greatly in different populations [24], are likely due to various ethnic backgrounds. This C allele of the *ENPP1* K121Q (rs1044498) variant increases the binding of *ENPP1* to the insulin receptor with subsequent enhanced IR and reduced kidney function in T2DM patients [42].

In the current study, we demonstrated an association between the C-risk allele of *ENPP1* K121Q (rs1044498) variant and the presence of albuminuria (≥30 mg/g) and reduced eGFR (<60 ml/min/1.73 m^2), together with an increased risk of developing DN in T2DM Egyptian patients. Previous studies in consistency with our findings had documented such an association in a population of Arab ancestry [43], in European and Asian populations [20], and in a meta-analysis of genetic association studies in different ethnic descents [23]. Nevertheless, the effect of this variant on the development of DN was opposed by some other studies. On the one hand, there was no evidence for the association of the *ENPP1* K121Q (rs1044498) variant and DN among African-American [44] and Brazilian individuals of African descent [45]. On the other hand, a South African Black population study assumed that A wild allele of the K121Q (rs1044498) variant, was the risk allele, that is associated with reduced eGFR and not the C allele [24].

The associations between *ENPP1* K121Q (rs1044498) and BMI are still under debate, and conflicting results have been reported. Our study could not reveal a consistent genetic association between these two variables. This was supported by the findings of several studies in European ancestry from the United States and Poland, and African-American individuals with and without T2DM [46], in Americans [47], Koreans [48], Chinese Han patients [25], north Indians [49], and Asian Indians [27], and was contrasted by finding a positive association with BMI in Moroccans [50], South African mixed ancestry [51], and European populations' studies [26].

This discordance among the various studies may be explained by the small sample sizes, the different ethnic backgrounds, and the different analytical approaches across the studies. Also, the interference of other polymorphisms or gene interactions may be a good explanation of these discrepancies. However, the main strength of this study is that it is a national study.

Conclusion

Our results point out that, among Egyptian patients with T2DM, those carrying AC/CC genotypes of the *ENPP1* K121Q (rs1044498) variant have an increased association with the development of DN. Early identification of this variant, that contributes to DN, may likely allow early satisfactory preventive, prophylactic, and therapeutic measures. Our results indicate that the *ENPP1* gene K121Q variant has no impact on BMI in Egyptian patients with T2DM. Controversial findings in different ethnic populations require multicentric studies recruiting larger sample sizes and met analyses to highlight

the underlying etiology, define heterogeneity between different groups, and may induce new prophylactic and therapeutic measures aiming this genetic variant.

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Conflicts of interest

There are no conflicts of interest.

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