

# Association of *ADIPOQ* Single-Nucleotide Polymorphisms with the Two Clinical Phenotypes Type 2 Diabetes Mellitus and Metabolic Syndrome in a Kinh Vietnamese Population

Steven Truong<sup>1,\*</sup>, Nam Quang Tran<sup>2,3,\*</sup>, Phat Tung Ma<sup>2,3</sup>, Chi Khanh Hoang<sup>3</sup>, Bao Hoang Le<sup>3</sup>, Thang Dinh<sup>3</sup>, Luong Tran<sup>3</sup>, Thang Viet Tran<sup>2,3</sup>, Linh Hoang Gia Le<sup>4</sup>, Hoang Anh Vu<sup>4</sup>, Thao Phuong Mai<sup>5</sup>, Minh Duc Do<sup>4</sup>

<sup>1</sup>Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA; <sup>2</sup>Department of Endocrinology, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam; <sup>3</sup>Department of Endocrinology, University Medical Center, Ho Chi Minh City, Vietnam; <sup>4</sup>Center for Molecular Biomedicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam; <sup>5</sup>Department of Physiology-Pathophysiology-Immunology, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam

\*These authors contributed equally to this work

Correspondence: Minh Duc Do, Center for Molecular Biomedicine, University of Medicine and Pharmacy at Ho Chi Minh City, 217 Hong Bang, District 5, Ho Chi Minh City, 700000, Vietnam, Tel +84 932999989, Email ducminh@ump.edu.vn

**Purpose:** Genetic factors play an important role in the development of type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS). However, few genetic association studies related to these disorders have been performed with Vietnamese subjects. In this study, the potential associations of *ADIPOQ* single nucleotide polymorphisms (SNPs) with T2DM and MetS in a Kinh Vietnamese population were investigated.

**Patients and Methods:** A study with 768 subjects was conducted to examine the associations of four *ADIPOQ* SNPs (rs266729, rs1501299, rs3774261, and rs822393) primarily with T2DM and secondarily with MetS. The TaqMan SNP genotyping assay was used to determine genotypes from subjects' DNA samples.

**Results:** After statistical adjustment for age, sex, and body mass index, the *ADIPOQ* SNP rs266729 was found to be associated with increased risk of T2DM under multiple inheritance models: codominant (OR = 2.30, 95% CI = 1.16–4.58), recessive (OR = 2.17, 95% CI = 1.11–4.26), and log-additive (OR = 1.32, 95% CI = 1.02–1.70). However, rs1501299, rs3774261, and rs822393 were not associated with risk for T2DM. Additionally, rs266729, rs3774261, and rs822393 were statistically associated with MetS, while rs1501299 was not. Haplotype analysis showed a strong linkage disequilibrium between the SNP pairs rs266729/rs822393 and rs1501299/rs3774261, and the haplotype rs266729(G)/rs822393(T) was not statistically associated with MetS.

**Conclusion:** The results show that rs266729 is a lead candidate SNP associated with increased risk of developing T2DM and MetS in a Kinh Vietnamese population, while rs3774261 is associated with MetS only. Further functional characterization is needed to uncover the mechanism underlying the potential genotype–phenotype associations.

**Keywords:** genetic association, Kinh Vietnamese, metabolic syndrome, type 2 diabetes mellitus

## Introduction

Metabolic syndrome (MetS) is characterized by a cluster of symptoms comprising of glucose intolerance, dyslipidemia, hypertension, and central obesity. Although definitions of MetS differ, it generally relates to insulin resistance or hyperinsulinemia.<sup>1–4</sup> Diabetes is a chronic metabolic disorder characterized by elevated levels of blood glucose, also known as hyperglycemia. Type 2 diabetes mellitus (T2DM) - with the distinct etiologies of insulin deficiency, insulin resistance, or both - accounts for approximately 90% of all cases of diabetes.<sup>5,6</sup> T2DM and MetS are common disorders

that share a similar insulin resistance pathophysiology. Additionally, the two conditions are often the result of obesity and sedentary lifestyle. Several studies have shown that subjects with MetS are highly likely to develop type 2 diabetes.<sup>7,8</sup> In tandem, T2DM and MetS are significant healthcare burdens contributing to morbidity and mortality globally, mainly through cardiovascular complications.<sup>9–11</sup>

Although environmental factors play an important part in the pathogenesis of these disorders, Asian individuals have been shown to have significant genetic predispositions to T2DM and MetS.<sup>12,13</sup> However, to date, no studies have examined the Vietnamese population, which totals more than 100 million inhabitants. This apparent lack of representation in genome research exacerbates health disparities,<sup>14–16</sup> underscoring the value of studying a Vietnamese sample population.

The *ADIPOQ* gene encodes adiponectin, an adipokine that regulates metabolic processes. Overall, serum adiponectin concentration correlates with heightened insulin sensitivity and improved islet  $\beta$ -cell function.<sup>17–20</sup> Conversely, low levels of adiponectin is associated with the development of MetS and T2DM.<sup>21,22</sup> Therefore, this study examined the potential associations of four single-nucleotide polymorphisms (SNPs) located in the *ADIPOQ* gene (rs266729, rs1501299, rs3774261, and rs822393) with T2DM and MetS in a Kinh Vietnamese population. While *ADIPOQ* SNPs have been reported to be associated with MetS and T2DM in South Asian, East Asian, and Caucasian populations,<sup>23–25</sup> this is the first study to investigate this association within the context of a Kinh Vietnamese population. The *ADIPOQ* SNPs in this study were chosen on the basis that previous studies have shown varying associations with T2DM and MetS, particularly among ethnically different populations. For example, studies have suggested that the *ADIPOQ* SNP rs266729 is associated with T2DM and MetS in East Asian populations and could be a functional SNP; meta-analysis supports this theory.<sup>26–28</sup> As rs266729 is located in the SP1-binding site of the *ADIPOQ* gene, it has been hypothesized that the G allele of rs266729 disrupts SP1-binding and consequently yields lower adiponectin expression in the body.<sup>29,30</sup> This hypothesis is supported by the work of Smetnev et al, who showed that in a population of Russian individuals, the G/G genotype of rs266729 results in lower levels of serum adiponectin compared to the C/C and C/G genotypes.<sup>31</sup> However, two different studies performed on European populations did not find rs266729 to be associated with T2DM.<sup>32,33</sup>

Additionally, 21 relevant studies of the *ADIPOQ* SNP rs1501299 have presented conflicting data on its association with T2DM; a meta-analysis by Han et al concluded that rs1501299 is not associated with T2DM risk, but this study did not consider inter-ethnic differences.<sup>26</sup> Similarly, rs3774261 confers differing risk of T2DM between ethnicities; it is associated with T2DM in Han Chinese and South Indian populations but not in white and black American populations.<sup>34–36</sup> Inter-ethnic differences are also evident with rs822393, which was shown by Ramya et al to confer a two-fold greater risk of T2DM in a population of South Indian individuals, while Yao et al found no such association in a population of ethnic Han northeast Chinese individuals.<sup>34,35</sup>

These discrepancies in T2DM and MetS risk from the *ADIPOQ* SNPs rs266729, rs1501299, rs3774261, and rs822393 point to potential inter-ethnic differences in genetic predisposition to the diseases. Thus, it is imperative to study the association of these SNPs with T2DM and MetS in a previously unstudied population, the Kinh Vietnamese.

## Materials and Methods

### Subject Recruitment

A total of 768 subjects who were all self-identified as Kinh Vietnamese were randomly recruited for this study. The study's protocol was approved by the institutional review board of the University of Medicine and Pharmacy at Ho Chi Minh City (HEC/IRB number 350/HĐĐĐ-ĐHYD), and informed written consent was obtained from all study subjects. T2DM subjects were selected if they had history of T2DM or were newly diagnosed with T2DM based on the American Diabetes Association 2020 criteria.<sup>5</sup> Among T2DM patients, further MetS diagnosis was made using the criteria provided by the Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults.<sup>2</sup> Patients were diagnosed with MetS when they had at least three among five following criteria: waist circumference over 40 inches (101 cm) (for men) or 35 inches (89 cm) (for women), blood pressure over 130/85 mmHg or currently on hypertension treatment, fasting triglyceride levels over 150 mg/

dl or currently on triglyceride-lowering treatment, fasting high-density lipoprotein (HDL) cholesterol levels less than 40 mg/dl (for men) or 50 mg/dl (for women), and fasting blood sugar (FPG) over 100 mg/dl or currently on diabetes treatment.

Exclusion criteria for T2DM cases were the following: (i) type 1 diabetes, (ii) liver dysfunction, (iii) use of substances affecting plasma glucose levels, and (iv) endocrine diseases that heighten plasma glucose levels. Control subjects were recruited among regular health checkup visitors to the hospital with the following exclusion criteria: (i) previous history of diabetes of any type, (ii) use of substances that affect plasma glucose levels, (iii) pregnancy, (iv) cancer, and (v) any other diseases which affect blood glucose levels. After selection, 376 subjects with T2DM were recruited and, of these, 239 participants fulfilled the criteria for MetS.

## Clinical and Laboratory Measurements

All subjects underwent a detailed physical examination and answered a survey soliciting information about their health as it pertained to the study. Anthropometric measurements included weight, height, waist circumference, hip circumference, systolic and diastolic blood pressure. Demographic information included age, sex, and duration of T2DM since diagnosis (for T2DM cases). Medication information, such as antihypertensive, antidiabetic, and lipid-lowering agents, was also documented.

Fasting (minimum 8 hours) blood samples were collected. Biochemical analyses were performed immediately using the Beckman Coulter AU2700 Chemistry Analyzer for FPG, HbA1c, total serum cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and creatinine levels.

## Genotyping

The remaining blood samples were stored at  $-20^{\circ}\text{C}$  until extracted for genomic DNA using the QiAmp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). SNP genotyping was performed using the TaqMan SNP genotyping assay (Thermo Fisher Scientific, Waltham, MA, USA) consisting proper forward, reverse primers, and fluorescently named MGB<sup>TM</sup> probes (FAM and VIC) to identify the alleles. PCR reactions were carried out using the 7900HT Fast Real-Time PCR System in separate 384-wells (Thermo Fisher Scientific, Waltham, MA, USA). PCR reactions were performed according to manufacturer's protocols in a total volume of 25  $\mu\text{L}$  (12.5  $\mu\text{L}$  of TaqMan universal PCR Master Mix, 0.625  $\mu\text{L}$  of TaqMan assay, and 6.875  $\mu\text{L}$  of milli-Q water and 5  $\mu\text{L}$  of DNA) for each SNP (rs266729, rs1501299, rs3774261, and rs822393). The thermal cycles consisted of  $63^{\circ}\text{C}$  for 1 min and  $95^{\circ}\text{C}$  for 3 min, followed by 40 cycles at  $95^{\circ}\text{C}$  for 15 sec and  $63^{\circ}\text{C}$  for 40 sec. Sample genotyping was identified based on the fluorescence signal detected.

## Statistical Analyses

For continuous variables, the distributions for baseline clinical measurements for case and control groups were compared using Student's independent two-tailed *t*-test. The use of the statistical test was based on the data's normality, as assessed by visual inspection and the Shapiro Wilk test for normality. The sex distribution in case and control groups was assessed using the Chi-Square test for independence. The ANOVA one-way test was used to investigate the differences of baseline clinical characteristics between genotypes for rs266729 and rs3774261.

Genotype frequencies were tested for Hardy-Weinberg equilibrium (HWE) using the goodness-of-fit  $\chi^2$  test. The web tool SNPstats was used to test for the association of the *ADIPOQ* SNPs rs266729, rs1501299, rs3774261 and rs822393 to T2DM and MetS under different inheritance models: codominant, dominant, recessive and log-additive.<sup>37</sup> Age, sex, and body mass index (BMI) were used as covariates for statistical adjustment in the models. Odds ratios (OR) were calculated with 95% confidence interval (CI). Haplotype frequency, linkage disequilibrium for each pair of alleles and the association between haplotypes and T2DM/MetS were analyzed using the Python SciKit-allel package.<sup>38</sup> Two-sided *P*-values  $<0.05$  were considered statistically significant.

## Results

### Clinical and Biochemical Characteristics of Study Subjects

Baseline demographic and clinical measurements for T2DM, MetS, and control subjects are presented in Table 1. For T2DM, statistically significant differences were found between the T2DM and T2DM-control group for age,

BMI, waist circumference, waist-to-hip ratio (WHR), HbA1c, FPG, systolic blood pressure (SBP), triglyceride levels, total cholesterol, HDL cholesterol, and LDL cholesterol ( $P<0.05$ ). On the other hand, there were no statistically significant differences between the two groups for diastolic blood pressure (DBP), serum creatinine levels, and sex.

For MetS, statistically significant differences were found between the MetS and MetS-control group for age, BMI, WHR, HbA1c, FPG, SBP, DBP, triglyceride levels, and HDL cholesterol. However, no statistically significant differences were found for total cholesterol, LDL cholesterol, and serum creatinine.

**Table 1** Baseline Clinical and Biochemical Characteristics of the Studied Population

	Type 2 Diabetes N=376	Metabolic Syndrome N=239	Controls N=392 (T2DM), 529 (MetS)	P-value
Males/females	150/226	67/172	159/233 242/287	0.908 <0.001*
Duration of disease (years)	5.71 ± 6.00	n/a	-	n/a
Age (years)	55.07 ± 11.90	54.04 ± 11.66	45.56 ± 12.64 48.49 ± 13.45	<0.001* <0.001*
BMI (kg/m <sup>2</sup> )	24.84 ± 3.59	25.71 ± 3.49	23.21 ± 3.38 23.24 ± 3.35	<0.001* <0.001*
Waist circumference (cm)	86.29 ± 9.69	88.85 ± 9.55	80.72 ± 9.45 81.00 ± 9.16	<0.001* <0.001*
WHR	0.92 ± 0.07	0.93 ± 0.064	0.89 ± 0.070 0.89 ± 0.070	<0.001* <0.001*
HbA1c (%)	8.25 ± 2.10	8.53 ± 2.10	5.69 ± 0.47 7.62 ± 2.08	<0.001* <0.001*
FPG (mmol/L)	8.59 ± 3.05	8.37 ± 3.12	5.52 ± 0.90 6.41 ± 2.25	<0.001* <0.001*
SBP (mmHg)	130.77 ± 17.93	135.71 ± 18.06	126.21 ± 16.33 125.16 ± 15.86	<0.001* <0.001*
DBP (mmHg)	78.2 ± 10.70	82.59 ± 11.27	80.0 ± 11.10 77.57 ± 10.36	0.188 <0.001*
Triglycerides (mmol/L)	2.48 ± 1.93	3.08 ± 2.18	2.05 ± 2.05 1.87 ± 1.78	<0.01* <0.001*
Total cholesterol (mmol/L)	4.72 ± 1.44	5.05 ± 1.46	5.37 ± 1.33 5.04 ± 1.41	<0.001* 0.931
HDL cholesterol (mmol/L)	1.12 ± 0.28	1.04 ± 0.20	1.27 ± 0.44 1.27 ± 0.42	<0.001* <0.001*
LDL cholesterol (mmol/L)	2.97 ± 1.06	3.23 ± 1.10	3.48 ± 0.89 3.23 ± 0.97	<0.001* 0.908
Serum creatinine (mg/dL)	0.87 ± 0.24	0.86 ± 0.22	0.88 ± 0.54 0.88 ± 0.49	0.895 0.488

**Note:** \*Statistically significant.

**Abbreviations:** BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

## Association of *ADIPOQ* SNPs with Type 2 Diabetes Mellitus

Genotype distributions for the SNPs rs266729, rs1501299, rs3774261, and rs822393 were all under HWE in the studied population, which includes T2DM, T2DM-control, MetS, and MetS-control groups (all P-values > 0.05) ([Supplementary Table 1](#)). Multiple inheritance models were used to assess statistically significant associations between genotypes and T2DM status: codominant ([Supplementary Table 2](#)), dominant ([Supplementary Table 3](#)), recessive ([Supplementary Table 4](#)), and log-additive ([Supplementary Table 5](#)). ORs were calculated with 95% confidence intervals (CI). To account for covariate effects, statistics were adjusted for age, sex, and BMI.

Only the SNP rs266729 showed a statistically significant association between genotypes and T2DM. The SNP showed statistically significant associations in three inheritance models: codominant (OR = 2.30, 95% CI = 1.16–4.58, P = 0.049), recessive (OR = 2.17, 95% CI = 1.11–4.26, P = 0.022), and log-additive (OR = 1.32, 95% CI = 1.02–1.70, P = 0.034) ([Table 2](#)). However, in the dominant inheritance model, the G allele for rs266729 did not confer risk of T2DM (OR = 1.27, 95% CI = 0.93–1.74, P = 0.13). On the other hand, rs1501299, rs3774261 and rs822393 did not show statistically significant associations with T2DM in all the inheritance models ([Supplementary Tables 2–5](#)).

## Association of rs3774261 with MetS

Because *ADIPOQ* regulates metabolism and lipid levels, the potential associations between the four *ADIPOQ* SNPs and MetS were also investigated. Using the same methodology as described above, statistically significant associations of rs3774261 with MetS were detected under different inheritance models ([Table 3](#)). On the other hand, rs266729 and rs822393 were found to be associated with MetS under the recessive inheritance model ([Table 4](#) and [Supplementary Table 8](#)). However, rs1501299 did not have statistically significant associations with MetS under any of the inheritance models ([Supplementary Tables 6–9](#)).

## Haplotype Analysis

Among the four SNPs examined in this study, strong linkage disequilibrium between the SNP pairs rs266729/rs822393 and rs1501299/rs3774261 was observed ([Figure 1](#)). Due to the borderline statistical associations between rs266729 and rs822393 with MetS, the haplotype rs266729/rs3774261 was further examined for association with MetS. However, the rs266729(G)/rs822393(T) haplotype was not found to be statistically associated with MetS ([Table 5](#)).

## Association of rs266729 and rs3774261 with Subjects' Characteristics

As rs266729 was associated with T2DM, and rs3774261 was associated with MetS, the rs266729 genotypes (CC, CG, GG) and rs3774261 genotypes (GG, GA, AA) were further analyzed with respect to subjects' clinical and biochemical

**Table 2** The Association of rs266729 with T2DM

Model	Genotype	Control (n)	T2DM (n)	Adjusted OR (95% CI) <sup>†</sup>	P-value <sup>‡</sup>
Co-dominant	C/C	226	198	1	0.049*
	C/G	148	146	1.16 (0.84–1.61)	
	G/G	18	32	2.30 (1.16–4.58)	
Dominant	C/C	226	198	1	0.130
	C/G, G/G	166	178	1.27 (0.93–1.74)	
Recessive	C/C, C/G	374	344	1	0.022*
	G/G	18	32	2.17 (1.11–4.26)	
Log-additive	—	—	—	1.32 (1.02–1.70)	0.034*

**Notes:** <sup>†</sup>Adjusted for sex, age, and BMI. N = 768. \*Statistically significant.

**Abbreviations:** OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus.

**Table 3** The Association of rs3774261 with MetS

Model	Genotype	Control (n)	MetS (n)	Adjusted OR (95% CI) <sup>†</sup>	P-value <sup>‡</sup>
Co-dominant	A/A	193	75	1	0.035*
	A/G	271	112	1.02 (0.70–1.49)	
	G/G	65	52	1.82 (1.11–2.98)	
Dominant	A/A	193	75	1	0.350
	A/G, G/G	336	164	1.19 (0.83–1.69)	
Recessive	A/A, A/G	464	187	1	0.009*
	G/G	65	52	1.79 (1.16–2.78)	
Log-additive	—	—	—	1.29 (1.01–1.65)	0.040*

Notes: <sup>†</sup>Adjusted for sex, age, and BMI. N = 768. \*Statistically significant.

Abbreviations: OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome.

**Table 4** The Association of rs266729 with MetS

Model	Genotype	Control (n)	MetS (n)	Adjusted OR (95% CI) <sup>†</sup>	P-value <sup>‡</sup>
Co-dominant	C/C	298	126	1	0.053
	C/G	205	89	0.95 (0.67–1.36)	
	G/G	26	24	2.20 (1.13–4.31)	
Dominant	C/C	298	126	1	0.640
	C/G, G/G	231	113	1.08 (0.78–1.51)	
Recessive	C/C, C/G	503	215	1	0.016*
	G/G	26	24	2.25 (1.17–4.32)	
Log-additive	—	—	—	1.20 (0.92–1.58)	0.180

Notes: <sup>†</sup>Adjusted for sex, age, and BMI. N = 768. \*Statistically significant.

Abbreviations: OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome.

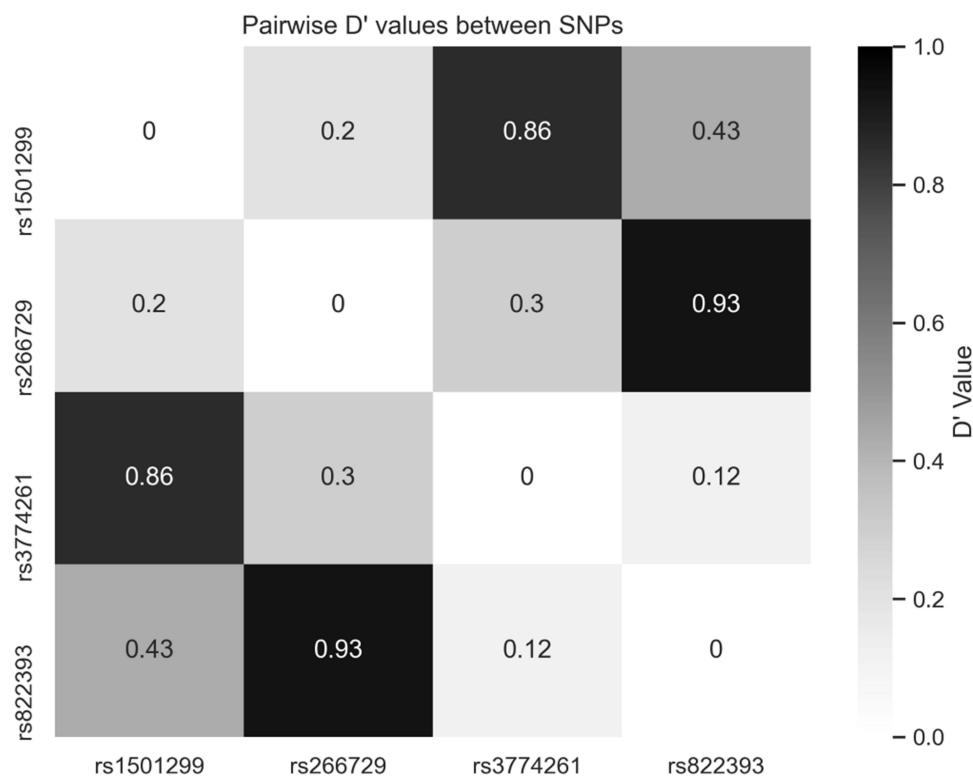
characteristics. In T2DM and MetS case and respective control subjects, there were no statistical differences observed in BMI, WHR, HbA1c, FPG, or triglyceride levels between rs266729 CC, CG, GG genotypes (Table 6) and rs3774261 GG, GA, AA genotypes (Table 7).

## Discussion

T2DM and MetS are polygenic disorders that present heavy healthcare burdens worldwide. Multiple risk loci of these disorders have been identified through genome-wide association studies.<sup>39,40</sup> Among contributing genetic factors, the *ADIPOQ* gene has been reported to be highly associated with T2DM, MetS, and obesity in various study populations.<sup>25,41–43</sup>

The results of this study show strong associations between the promoter variants rs266729 to T2DM and rs3774261 to MetS. This finding corroborates with the well-documented effect of rs266729 on T2DM risk in East Asian populations.<sup>26</sup> The finding that rs3774261 is associated with MetS but not T2DM is quite a novel finding, with only one previous study reporting this association in a population of elderly Han Chinese.<sup>44</sup> This result emphasizes the importance of investigating previously unstudied populations.





**Figure 1** Linkage disequilibrium between allele pairs of rs266729, rs1501299, rs3774261, and rs822393.

Another interesting observation is that rs1501299 was not found to be associated with either T2DM or MetS in the studied Kinh Vietnamese population. Contrary to this observation, this variant has been found to have close associations with the obesity and T2DM phenotypes in several studies of African, Asian, and Caucasian populations.<sup>45–48</sup> Notably, rs1501299 showed a contradicting protective role against obesity in a Tunisian population.<sup>49</sup> These findings once again highlight the important potential effects of ethnicity on genetic studies, emphasizing the unique genetic characteristics of the Kinh Vietnamese in terms of genetic variation and disease association.<sup>50–53</sup>

It has been shown that adiponectin concentration is highly heritable and can be regulated by *ADIPOQ* genetic variants.<sup>54</sup> The associations between *ADIPOQ* SNPs and major adverse phenotypes, such as diabetes, obesity, MetS, and even coronary heart disease, are considered to be the result of hypoadiponectinemia, given the important role of adiponectin in regulating metabolism and anti-inflammatory functions. Apart from the disruption of SP1-binding in the promoter region by rs266729, the association of rs3774261 with hypoadiponectinemia is still not well understood. Interestingly, this variant has been shown to be associated with eating behavior and can affect the results of nutritional

**Table 5** The Association of Haplotype rs266729/rs822393 with MetS

rs266729	rs822393	Frequency	Adjusted OR (95% CI) <sup>†</sup>	P-value <sup>†</sup>
C	C	0.586	1.00	—
G	T	0.246	1.26 (1.01–1.73)	0.110
C	T	0.158	1.08 (0.77–1.47)	0.660
G	C	0.010	0.72 (0.54–4.51)	0.600

**Notes:** <sup>†</sup>Adjusted for sex, age, and BMI. N = 768.

**Abbreviations:** OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus.

**Table 6** The Association of rs266729 with Clinical and Biochemical Characteristics in T2DM and Control Subjects

Characteristics	rs266729											
	T2DM (N=376)				Controls (N=392)				Studied Population (N=768)			
	CC	CG	GG	ANOVA P-value	CC	CG	GG	ANOVA P-value	CC	CG	GG	ANOVA P-value
BMI (kg/m <sup>2</sup> )	24.67 ± 3.68	25.04 ± 3.51	24.93 ± 3.29	0.63	23.05 ± 3.09	23.58 ± 3.76	22.31 ± 3.23	0.17	23.80 ± 3.48	24.30 ± 3.71	23.99 ± 3.51	0.18
WHR	0.91 ± 0.069	0.92 ± 0.072	0.91 ± 0.067	0.50	0.88 ± 0.064	0.89 ± 0.078	0.88 ± 0.045	0.21	0.90 ± 0.068	0.91 ± 0.076	0.90 ± 0.062	0.09
HbA1c (%)	8.23 ± 2.07	8.26 ± 2.20	8.39 ± 1.82	0.92	5.64 ± 0.46	5.74 ± 0.46	5.83 ± 0.39	0.78	8.01 ± 2.11	8.08 ± 2.22	8.17 ± 1.89	0.89
FPG (mmol/L)	8.49 ± 3.01	8.69 ± 3.22	8.71 ± 2.39	0.82	5.55 ± 1.06	5.47 ± 0.61	5.55 ± 0.77	0.68	6.93 ± 2.65	7.07 ± 2.81	7.57 ± 2.48	0.28
SBP (mmHg)	131.15 ± 18.39	129.61 ± 16.67	133.69 ± 20.01	0.46	126.31 ± 16.47	125.77 ± 16.36	128.72 ± 13.79	0.76	128.57 ± 17.56	127.68 ± 16.62	131.90 ± 18.17	0.27
DBP (mmHg)	78.34 ± 11.48	77.83 ± 9.49	78.84 ± 10.36	0.85	79.80 ± 10.99	80.50 ± 11.44	79.17 ± 8.45	0.79	79.12 ± 11.24	79.17 ± 10.60	78.96 ± 9.72	0.99
Triglycerides (mmol/L)	2.44 ± 1.67	2.53 ± 2.32	2.49 ± 1.33	0.91	1.79 ± 1.21	2.02 ± 2.42	1.71 ± 1.09	0.67	2.22 ± 1.65	2.33 ± 2.49	2.22 ± 1.32	0.77
Total cholesterol (mmol/L)	4.71 ± 1.46	4.72 ± 1.42	4.74 ± 1.44	1.00	5.30 ± 1.10	5.47 ± 1.63	5.34 ± 1.19	0.50	5.02 ± 1.32	5.10 ± 1.58	4.94 ± 1.39	0.70
HDL cholesterol (mmol/L)	1.11 ± 0.26	1.16 ± 0.33	1.07 ± 0.23	0.19	1.26 ± 0.44	1.29 ± 0.45	1.28 ± 0.26	0.80	1.19 ± 0.37	1.22 ± 0.40	1.14 ± 0.26	0.27
LDL cholesterol (mmol/L)	2.94 ± 1.10	3.04 ± 1.01	2.85 ± 0.99	0.58	3.48 ± 0.88	3.48 ± 0.89	3.50 ± 1.00	1.00	3.23 ± 1.02	3.26 ± 0.98	3.07 ± 1.04	0.49

**Abbreviations:** BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.



**Table 7** The Association of rs3774261 with Clinical and Biochemical Characteristics in MetS and Control Subjects

Characteristics	Rs3774261											
	MetS (N=239)				Controls (N=529)				Studied Population (N=768)			
	GG	GA	AA	ANOVA P-value	GG	GA	AA	ANOVA P-value	GG	GA	AA	ANOVA P-value
BMI (kg/m <sup>2</sup> )	25.05 ± 3.47	26.06 ± 3.42	25.64 ± 3.53	0.22	24.29 ± 3.54	23.17 ± 3.20	22.98 ± 3.40	0.062	24.63 ± 3.53	24.01 ± 3.52	23.73 ± 3.64	0.074
WHR	0.94 ± 0.81	0.93 ± 0.057	0.93 ± 0.060	0.58	0.88 ± 0.059	0.89 ± 0.068	0.89 ± 0.077	0.46	0.91 ± 0.075	0.90 ± 0.068	0.90 ± 0.074	0.55
HbA1c (%)	8.43 ± 1.83	8.48 ± 1.93	8.69 ± 2.51	0.79	7.42 ± 1.95	7.58 ± 1.88	7.78 ± 2.39	0.93	8.03 ± 1.94	7.98 ± 1.95	8.17 ± 2.48	0.73
FPG (mmol/L)	8.47 ± 2.88	8.66 ± 3.53	7.88 ± 2.49	0.24	6.51 ± 2.67	6.45 ± 2.30	6.33 ± 2.01	0.78	7.38 ± 2.93	7.10 ± 2.90	6.77 ± 2.27	0.095
SBP (mmHg)	139.92 ± 18.08	134.10 ± 18.12	135.17 ± 17.51	0.15	123.91 ± 14.00	125.69 ± 16.06	124.84 ± 16.12	0.37	131.03 ± 17.82	128.15 ± 17.12	127.74 ± 17.16	0.21
DBP (mmHg)	83.48 ± 9.29	82.13 ± 11.85	82.67 ± 11.60	0.78	76.80 ± 9.42	78.50 ± 10.67	76.51 ± 10.11	0.61	79.77 ± 9.94	79.56 ± 11.15	78.24 ± 10.91	0.25
Triglycerides (mmol/L)	3.18 ± 3.03	3.14 ± 2.09	2.94 ± 1.50	0.79	1.94 ± 1.51	1.78 ± 1.28	1.98 ± 2.37	0.61	2.50 ± 2.40	2.19 ± 1.69	2.26 ± 2.20	0.34
Total cholesterol (mmol/L)	5.01 ± 1.46	5.02 ± 1.37	5.14 ± 1.58	0.85	4.91 ± 1.32	5.03 ± 1.13	5.11 ± 1.76	0.83	4.96 ± 1.38	5.03 ± 1.20	5.12 ± 1.71	0.56
HDL cholesterol (mmol/L)	1.05 ± 0.22	1.06 ± 0.21	1.00 ± 0.18	0.18	1.26 ± 0.31	1.27 ± 0.41	1.29 ± 0.45	0.97	1.16 ± 0.30	1.20 ± 0.38	1.21 ± 0.41	0.54
LDL cholesterol (mmol/L)	3.08 ± 1.11	3.22 ± 0.98	3.35 ± 1.23	0.39	3.12 ± 0.97	3.27 ± 0.92	3.19 ± 1.03	0.64	3.11 ± 1.03	3.26 ± 0.94	3.24 ± 1.09	0.36

**Abbreviations:** BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

intervention.<sup>55,56</sup> Additionally, the lack of linkage disequilibrium between the SNP pairs rs266729 and rs3774261 suggests that these two SNPs may regulate the adiponectin level by independent mechanisms.

On the other hand, the pair rs266729 and rs822393 was found to be in strong linkage disequilibrium. In this study, no association between the rs266729(G)/rs822393(T) haplotype and MetS was observed. However, both rs266729 and rs822393 have been shown to be significantly associated with hypoadiponectinemia in the literature.<sup>36</sup> Altogether, the data suggest that these SNPs may regulate adiponectin levels by the same mechanism, and the combination of rs266729 (G)/rs822393(T) may have compounding effects on serum adiponectin levels in the studied population. The comparison of clinical and biochemical parameters between rs266729 genotypes in T2DM and rs3774261 in MetS group showed no statistical differences. This observation is consistent with previous studies in which *ADIPOQ* SNPs were not statistically associated with biochemical parameters except for insulin concentration and homeostasis model assessment index for insulin resistance.<sup>57,58</sup>

Nevertheless, the present study carries several limitations. First, the adiponectin level was not measured due to the lack of reliable facilities; hence, the associations between the SNPs and adiponectin levels were not elucidated. Second, the small sample size may affect the study's statistical power. However, future meta-analyses and studies building on the present study will help reconcile the numerous inconsistent findings in the literature for the *ADIPOQ* SNPs studied.

## Conclusions

To our knowledge, this is the first study of its kind performed with a population of Kinh Vietnamese individuals, underscoring its importance in the wider context of genomics research. Nonetheless, additional replication or further expanded studies with larger sample sizes are required to form stronger conclusions. Future functional studies are also needed to understand the biology underlying these potential genotype–phenotype associations. Also, going forward, additional variants should be investigated to pinpoint the differences in genetic predispositions to T2DM and MetS between populations globally.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request: please contact [ducminh@ump.edu.vn](mailto:ducminh@ump.edu.vn).

## Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (FWA registered number: FWA00023448). Approval number: 350/HĐĐĐ-ĐHYD on May 26th, 2020 and informed consent was taken from all individual participants.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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