ASSOCIATION OF *ADIPOQ* (*rs2241767)* AND *METRNL* (*rs147617313)* GENE POLYMORPHISMS WITH TYPE 2 DIABETES MELLITUS IN THE VIETNAMESE POPULATION: A CASE – CONTROL STUDY

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Adipokines derived from adipose tissue have been proven to participate in many metabolic pathways in the body. Adipokine dysregulation has been considered an important cause of many metabolic diseases, such as Type 2 Diabetes Mellitus (T2DM). Our research investigated the association between the two single-nucleotide polymorphisms of the ADIPOQ and METRNL genes with T2DM. A case-control study was conducted with 260 T2DM patients and 260 healthy controls. The ADIPOQ variant (rs2241767) and the METRNL variant (rs147617313) were determined based on polymerase chain reaction-restriction fragment length polymorphism. The rs147617313 locus of the METRNL gene showed only one homozygous genotype, CC. In the rs2241767 locus of the ADIPOQ gene, the genotype frequencies in the case group (AA: 41%, AG: 50%, GG: 9%) were similar to those in the control group (AA: 47%, AG: 40 %, GG: 13%). The AG genotype was associated with an increased risk of T2DM in the additive model (OR = 1.4; 95%CI: 1.0 – 2.09; p = 0.046). Of the two single-nucleotide polymorphisms, rs2241767 and rs147617313, only rs2241767 was associated with the risk of type 2 Diabetes Mellitus in Vietnamese people.

Keywords: Adiponectin, variant, Subfatin, metabolic syndrome.

I. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) represents a significant public health issue. Identifying individuals at risk for early detection, prevention, and intervention is crucial for improving public health outcomes. In addition to well-established risk factors such as lifestyle and environmental influences, a strong genetic component is associated with the development of Type 2 Diabetes Mellitus.[1,2] Some evidence suggest that genetic variants might increase the risk of developing the disease by 10 – 30%.[3] The genetic variants might affect the pathogenesis of type 2 diabetes through two main pathways: (1) impairing beta cell function; and (2) increasing insulin resistance. These variants have been shown to be related to obesity, lipodystrophy, fat metabolism and liver metabolism.[4] Genetics, combined with multiple genetic variants in a polygenic score, has been proven to play a crucial role in disease pathogenesis. Understanding the mechanisms of action and utilizing polygenic scores could enhance the ability to predict disease risk while providing a foundation for targeted treatments.[5]

Adipose tissue and lipid metabolism were important in the pathogenesis of T2DM. Adipokines, factors secreted from adipocytes, directly affected their activity through autocrine or paracrine mechanisms and the whole body's homeostasis through the circulatory system.

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Adipokine dysregulation could contribute to obesity-related disorders, metabolic and cardiovascular diseases.[8] Researchers were also interested in adipose tissue gene variant studies due to the unclear mechanisms of action. In this study, we selected two adipokines believed to have many positive effects on improving insulin resistance: *ADIPOQ* and *METRNL*. The protein Adipoq promoted insulin action by enhancing glucose uptake in muscle and fat cells and had anti-inflammatory effects by regulating the activity of phagocytes and endothelial cells. Low Adipoq levels were strongly associated with insulin resistance, obesity, and increased risk of type 2 diabetes.[9] Several single-nucleotide polymorphisms (SNPs) in the *ADIPOQ* gene had been identified as influencing Adipoq levels and the risk of type 2 diabetes.[10,11] The protein Metrnl regulated thermogenesis in brown adipose tissue and enhanced adipocyte mitochondrial function and energy expenditure; regulated insulin sensitivity and inflammation.[12,13] These two single-nucleotide polymorphisms would provide helpful information about their role in type 2 Diabetes Mellitus and the gene characteristics in Vietnamese people.

II. MATERIALS AND METHODS

1. Subjects

Selection criteria

All the subjects participated in the study when patients at 103 Military Hospital, Hanoi, Vietnam, from April 2022 to August 2024. The inclusion criteria for Type 2 Diabetes Mellitus (T2DM) patients (case group) were based on the guidelines for type 2 Diabetes Mellitus diagnosis by the American Diabetes Association 2022. The control group was chosen from healthy people of similar ages.

Exclusion criteria

- Patients with type 1 DM, endocrinological disorder diseases such as thyroid disease; chronic kidney disease; chronic liver diseases; cancer.

- T2DM patients having complications, anemia, hemoglobinopathies such as thalassemia and B12 deficiency.

2. Methods

A case-control study was conducted with 260 Type 2 Diabetes Mellitus (T2DM) patients and 260 healthy controls. Due to logistical constraints, a convenience sample size was employed. This approach might introduce selection bias, which is acknowledge as a limitation of this study. T2DM patients were randomly chosen, and healthy controls were selected to have similar ages. The family history of diabetes, history of dysregulated lipids, biochemistry test, height, weight, blood systolic, and diastolic data were collected at the hospital admission. The biochemistry test, including fasting blood glucose, urea, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and uric acid, were analyzed in the AU5800 analyzer (Beckman Coulter, USA). The HbA1c was determined by the high-performance liquid chromatography method on Premier 9200 (Trinity Biotech, USA). The BMI was calculated as the formular:

BMI = Weight (Kilograme)/ Height^2 (Metre)

The insulin resistance was estimated through the Metabolic Score for Insulin Resistance index:

METS-IR (Metabolic Score for Insulin Resistance)= ln {(2 x fasting glucose level (mg/dl)) + Triglycerid (mg/dl)} x BMI)/(ln (HDL-c (mg/dl))).[14]

SNP genotyping

Two milliliters of EDTA blood sample were collected from each participant to extract the DNA from leukocyte by the QIAamp DNA Blood

Kits – Genomic DNA Extraction (250) Cat no. / ID. 51106. The purity of the extracted DNA was checked by measuring its optical density (OD). The data about the SNP was based on the data of NCBI.

The single nucleotide polymorphisms of ADIPOQ *rs2241767* and METRNL *rs147617313* were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The PCR for determination of *rs2241767* was pre-degenerated at 95°C for 3 mins, followed by 35 cycles of denaturation at 95°C for 35s, annealing at 58 °C for 40s, elongation at 72°C for 45s, final elongation at 72°C for 5 mins. The PCR forward primer was *TTATGTTAACCATAAGCAACCTTA*. The PCR reverse primer was *TAGTAACCACCAACAGAGCC*. The PCR products were run on 1.5% agarose gels electrophoresis. The cleavage reaction was carried out at 37°C for 3 hours with enzyme *BspTI (AflII)* (Thermo Fisher Scinetific, USA). The product of cleavage reaction were run on 3% agarose gel electrophoresis. In the gel images, two fragments of 316 and 23 bp products were showed with AA genotype, three fragments of 339, 316 and 23 bp products were showed with AG genotype, and one fragment of 339 bp product were showed with GG genotype.

The PCR for determination of *rs147617313* was pre-degenerated at 95°C for 3 mins, followed by 35 cycles of denaturation at 95°C for 30s, annealing at 59°C for 35s, elongation at 72 °C for 45s, final elongation at 72°C for 5mins. The PCR forward primer was *GAATTTCCACGCTAGATGGC*. The PCR reverse primer was *GAAGAGGAAGTCGCCATGCC*. The PCR products were run on 1.5% agarose gels electrophoresis. The cleavage reaction was carried out at 37°C for 3 hours with enzyme *HpaII (MspI)* (Thermo Fisher Scinetific, USA). The product of cleavage reaction was run on 3% agarose gel electrophoresis with marker 100bp. In the gel images, three fragments of 248 bp, 66 bp and 23 bp products were showed with CC genotype, four fragments of 314, 248, 66 and 23 bp products were showed with CT genotype, and two fragment of 314 bp and 23 bp products were showed with TT genotype.

10% of all the samples were randomly chosen for Sanger Sequencing to confirm the PCR-RFLP results. The forward primers for Sanger sequencing of *rs2241767* and *rs147617313* were *TGGCCTCTTTCATCACAGACC*, and *GAATTTCCACGCTAGATGGC* respectively.

Statistics analysis

The parametric variables were presented in mean and standard deviation. The non-parametric variables were presented in the median and interquartile ranges. The t-student test was used to compare two parametric variables. The Man-Whitney test was used for non-parametric variables. The Chi-square test was used to compare two propositions. Hardy Weinberg Equilibrium Test was done for both SNPs to analyze the equilibrium. Statistical analysis was performed using JASP software 0.19.3 (University of Amsterdam, Neitherland). Logistic regression was used to evaluate the model for the diagnosis of disease.

Research site

The research was performed at 103 Military Hospital, Vietnam Military Medical University.

3. Research ethics

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Hanoi Medical University Institutional Ethical Review Board with reference number 686/GCN-HĐĐĐNCYSH-ĐHYHN on the date 04 June 2022.

III. RESULTS

1. The characteristic of the subjects

Table 1. The characteristic of the subjects

	Case group (T2DM patients group) (n = 260)	Control Group (healthy group) (n = 260)	p- value
Gender (n,%) Male Female	260 (100) 149 (*57.31*) 111 (*42.69*)	260 (100) 106 (*40.76*) 154 (*59.23*)	> 0.05*
Age (year)	56.31 ± 11.37	55.62 ± 8.62	> 0.05**
Height (meter)	1.59 ± 0.07	1.61 ± 0.07	< *0.05***
Weight (kilogram)	61.73 ± 10.35	59.51 ± 7.79	< *0.05***
BMI (kg/m^2)	24.23 ± 3.20	22.82 ± 3.39	< *0.05***
Blood Systolic (mmHg)	126.75 ± 26.91	117.12 ± 26.20	< *0.05***
Blood Diastolic (mmHg)	75.81 ± 15.27	72.38 ± 8.22	< *0.05***
Fasting blood glucose (mmol/l)	9.86 ± 4.13	5.04 ± 0.36	< *0.001***
HbA1c (%)	8.48 ± 2.02	5.59 ± 0.30	< *0,001***
Urea (mmol/l)	5.64 ± 1.55	5.11 ± 1.24	< *0.001***
Creatinine (µmol/l)	83.33 ± 23.30	75.00 ± 13.92	< *0.001***
Total Cholesterol (mmol/l)	5.46 ± 1.67	5.08 ± 0.86	< *0.05***
HDL-Cholesterol (mmol/l)	1.17 ± 0.36	1.33 ± 0.29	< *0.001***
LDL-Cholesterol (mmol/l)	3.16 ± 1.00	3.26 ± 0.77	0.99**
Triglyceride (mmol/l)	3.26 ± 3.08	1.80 ± 1.09	< *0.001***
Uric acid (mmol/l)	336.37 ± 93.27	315.32 ± 81.80	< *0.05***
MET-IR	40.38 ± 5.97	33.64 ± 5.33	< *0.001***

*SD: Standard devision; BMI: body mass index; METS-IR (Metabolic Score for Insulin Resistance); * Chi-Square test; ** t-Student test*

In this study, 260 individuals with type 2 diabetes mellitus (T2DM) and 260 healthy controls participated. Age, gender, and LDL-cholesterol levels were similar between two groups. However, the T2DM group exhibited significantly higher height, weight, BMI, fasting blood glucose, urea, creatinine, total cholesterol, triglycerides, uric acid, and MET-IR than the control group. HDL-cholesterol was significantly lower in the T2DM group.

2. Genotype distribution of two SNPs

The results of the PCR-RFLP method showed a 100% concordance rate with the Sanger Sequencing results for all the randomly selected samples.

Table 2. Genotype distribution of *rs147617313* (*METRNL* gene)

	Genotypes n(%)			Alleles n(%)	
	CC	**CT**	**TT**	**C**	**T**
Case (n = 260)	260 (100)	0 (0)	0(0)	260 (100)	0 (0)
Control (n = 260)	260 (100)	0 (0)	0(0)	260 (100)	0 (0)
Total (n = 520)	520 (100)	0 (0)	0 (0)	520 (100)	0 (0)

The *rs147617313* locus of the METRNL gene showed only one homozygous genotype, CC.

Table 3. Genotype distribution of *rs2241767* (*ADIPOQ* gene)

	Genotypes n *(%)*			Alleles n *(%)*		p-value	HWE
	AA	**AG**	**GG**	**A**	**G**		
Case (n = 260)	107 (41)	131 (50)	22 (9)	172 (66)	88 (34)	0.082	+
Control (n = 260)	122 (47)	103 (40)	35 (13)	174 (67)	86 (33)	0.317	+
Total (n = 520)	229 (43)	234 (35)	57 (22)	346 (67)	174 (33)	0.809	+

HWE: Hardy Weinberg equilibrium; "+": Complies with HWE equilibrium law; p-value was calculated by Chi Square test; p value was significant at p < 0.05

The frequencies of three genotypes, AA, AG, and GG in the *rs2241767* locus of the ADIPOQ gene were 41%; 50%; and 9%, respectively, in the case group; and 47%, 39.5%, and 13.4%, respectively, in the control group. There was no statistically significant difference in the genotype frequencies between the case and control groups.

3. The risk of type 2 Diabetes Mellitus of the genotype model of *rs2241767*

Table 4. The odd ratio risk of type 2 Diabetes Mellitus of the genotype model of *rs2241767*

Model	Case (n = 260)	Control (n = 260)	OR	95%CI	p*
Additive					
AA	107	122	1		
AG	131	103	1.45	1 – 2.09	*0.046*
GG	22	35	0.71	0.39 – 1.29	
Dominant					
AA + AG	238	225	1		
GG	22	35	0.59	0.33 – 1.04	0.06
Recessive					
AG + GG	153	138	1		
AA	107	122	1.26	0.89 – 1.79	0.18

** Chi-square test; p value was significant at p < 0.05*

In the additive model, the AG genotype was associated with an increased risk of T2DM (OR = 1.4; 95%CI: 1.0 – 2.09; *p = 0.046*).

Table 5. The logistic regression model for estimating the type 2 Diabetes Mellitus risk

Variables	Odds Ratio (OR)	95% CI	p-value
Age	1.02	0.99 – 1.04	0.12
Gender (Male)	2.51	1.60 – 3.94	*< 0.001*
BMI	0.14	0.06 – 0.34	*< 0.001*
Height	0.52	0.40 – 0.67	*< 0.001*
Weight	2.23	1.57 – 3.17	*< 0.001*
Dysregulation lipid	$3.75x\ 10^7$	0.00 – ∞	0.98
Family history	$4.27\ x\ 10^7$	0.00 – ∞	0.98
rs2241767 genotype AG (vs AA)	1.56	1.03 – 2.35	*0.035*
rs2241767 genotype GG (vs AA)	0.72	0.34 – 1.50	0.38

CI: confidence interval; BMI: body mass index; p value was significant at p < 0.05

Logistic regression model showed the gender, BMI, weight, height and genotype AG of locus *rs2241767* were the risk of T2DM.

IV. DISCUSSION

Some single nucleotide polymorphisms of *ADIPOQ* were reported to play a role in the T2DM and Metabolic Syndrome in the Vietnamese population.[15] This research observed another variant in *ADIPOQ* (*rs2241767*) and one in the *METRNL* gene (*rs147617313*). Data regarding these two variants in the Vietnamese population were limited. Results obtained from these two variants would enrich the Vietnamese gene data. Moreover, the role of the variant in the T2DM mechanism would be clearer.

The *rs147617313* variant was a missense variant that could influence the amino acid change, structure, and function. The study found that the *rs147617313* locus of the *METRNL* gene has only one homozygous genotype CC. This result was similar to the data published in the NCBI for *rs147617313.*[16,17] Besides, the data about the *METRNL* gene needs to be improved further because of the role of Metrnl protein in the metabolic pathways. Mainly, the *METRNL* gene was located at 17q25.3 on chromosome a region that might contain many essential genes with a wide range of pathological effects, such as cardiovascular disease in people with diabetes, hypertension, Myoyama disease (a rare disease that causes cerebral embolism), coronary artery disease, bipolar disorder, prostate cancer.[18-22]

The *ADIPOQ rs2241767* variant was in the intron 2 field of the gene. Although the intron variants did not influence the structure of the protein, they influenced the splicing, transcription, and translation. Many SNPs in the intron region of the *ADIPOQ* gene have been correlated to T2DM.[11] Genome data of *rs2241767* showed that the distribution rate of allele A was more dominant in most races (European, Asian, and Hispanic American). In contrast, allele G had a higher rate in white and black people living in the US and non-Hispanic people. Genotype AA was higher in Europe, China, Arab, and our study, while genotype

AG had a higher rate in the racial groups in the America and Japan.[10,23-26] Thus, at this locus, there were differences in the frequency of genotype and allele distribution between different ethnic groups. In the Asian region, our research results were similar to those of the Han people in China. In our study, in the group with type 2 diabetes, the proportion of AG genotype accounted for up to 50% and was associated with an increased risk of diabetes with OR = 1.4 (95% CI: 1 - 2.09; *p = 0.046*). The OR value in this study was not adjusted for age and gender to limit multicollinearity, as both age and gender had been shown to have a substantial impact on the disease model.

Additionally, the sample size in this study was relatively small. Moreover, type I errors were likely to occur with small sample size. However, since only a single variant *rs2241767* was analyzed in the study, a significance level of 0.05 was sufficient to control this type I error. Similaly, the study by Du et al. on 1105 people with type 2 diabetes and 1107 healthy people of Han ethnicity in China showed that in the group with high BMI (overweight and obese group), the AG genotype at position *rs2241767* accounted for a high proportion of up to 46%; and increased the risk of diabetes with OR = 1.32 (95%CI: 1.03 - 1.69; *p = 0.02*).[27] However, due to the diversity of genotypes in ethnic populations, some studies had given different results. Cui et al., and Mtiraoui et al. showed no association between this SNP (*rs2241767*) and the T2DM.[28,29]

It could be seen that the demonstration of the association of the *rs2241767* polymorphism with the risk of type 2 diabetes remained inconclusive, with insufficient strong evidence. However, this polymorphism was still worth considering in type 2 diabetes. First, many studies combining gene polymorphisms with Adipoq protein concentrations showed that the *rs2241767* gene polymorphism was associated with Adipoq concentrations. Specifically, the study of Du et al. showed that the AG+GG genotype had a statistically significantly lower mean Adipoq concentration than the AA genotype in the group with type 2 diabetes (n = 1105).[27] The study of Zusi et al. on 794 people with newly diagnosed type 2 diabetes showed that the group carrying the G allele at the *rs2241767* polymorphism had a lower circulating Adipoq concentration than the group carrying the A allele, the difference was statistically significant with *p = 0.038*.[30] With quite large sample sizes, two studies above showed a decrease in Adipoq concentration corresponding to the groups carrying alleles or genotypes with a higher risk of the disease. The decreasing Adipoq was completely consistent with the pathogenic mechanisms of Adipoq in diabetes. The second reason was because many different studies have shown some associations of the *rs2241767* gene polymorphism with factors in the pathological chain with type 2 diabetes such as metabolic syndrome (central obesity, polycystic ovary syndrome, non-alcoholic liver disease), atherosclerosis, glomerular disease or even the risk of recurrent miscarriage or cancer.[31-33] Many studies had shown that the genetic interaction between the *rs2241767* polymorphism and other polymorphisms of the *ADIPOQ* gene could increase the risk of disease, such as *rs2241767* associated with the *rs1063537* polymorphism can increase the risk of progression of glomerular disease in men with type 2 diabetes in Taiwan;[34] or *rs2241767* combined with *rs3865188* increases the risk of colorectal cancer in Koreans;[35] or *rs2241767* combined with *rs1501299* increases the risk of recurrent miscarriage.[24] Previous polymorphism studies in various diseases

were limited to cross-sectional designs, lacking direct mechanistic evidence and corroboration in animal models. Furthermore, limitations in analyzing gene-gene and gene-environment interactions hindered a comprehensive understanding of disease etiology.

In the logistic regression with many factors, the OR of AG *rs2241767* had risen from 1.04 to 1.56. A combination of multiple factors, especially with a known factor such as anthropometric, and the gene variants would increase the predictive ability for the low risk-subject. For example, a very high proportion of people in East or Southeast Asia with type 2 diabetes (up to 60%) were of normal weight or thin. Even in Western countries, this figure was around 25%. However with multi-locus genetic assessment, it was possible to change the relative and absolute risks in BMI groups and gender. In these subjects, the genetic risk factors were stronger. In a study in the US, each increase in the genetic multi-locus could help diagnose up to 1.3 years earlier, the rate of early diagnosis also increased.[36]

This study also faced some limitations. First, the sample size of this research was quite small therefore, the power of confidence in the results was limited. This result could be combined with additional results in a multicenter or meta-analysis study to increase the power. Secondly, the technical constraints of the PCR-RFLP method, chosen for its accuracy despite its simplicity, restricted analysis to a single variant per gene. Analyzing only one variant prevented assessment of linkage disequilibrium and its potential impact on disease mechanisms. With the new technology of the next gene sequencing, the information about the whole gene would be clearer and more SNPs would be suggested for diagnosis. Especially, time would be saved. Thirdly, the absence of protein concentration data made it difficult to establish a clear link between the variant and its functional role in the disease.

V. CONCLUSIONS

Of the two single-nucleotide polymorphisms, *rs2241767* and *rs147617313,* only *rs2241767* was associated with the risk of type 2 Diabetes Mellitus in Vietnamese people.

Acknowledgment and conflict of interest declaration

The authors declare no conflict of interest.

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