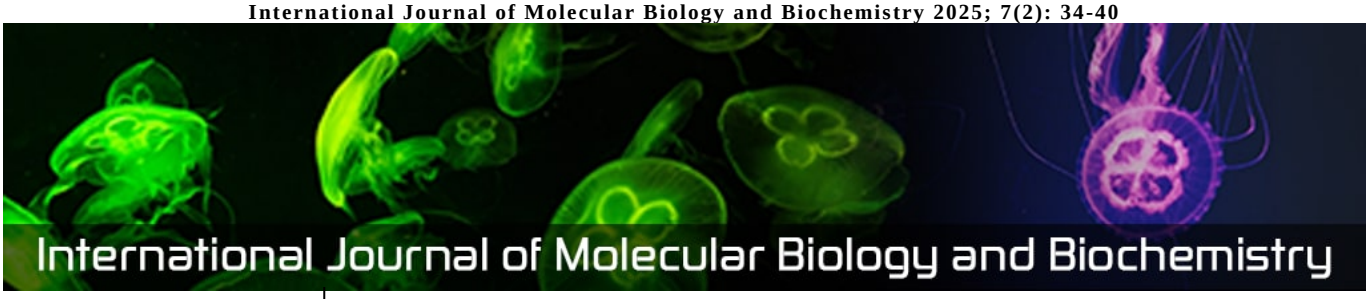


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# Adiponectin gene polymorphism and transcription insights in obesity of Myanmar male population

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**Abstract**
**Background:** Obesity is a multifactorial disorder influenced by environmental and genetic factors. Adiponectin, encoded by the *ADIPOQ* gene, regulates glucose metabolism, fatty acid oxidation, and insulin sensitivity, with circulating levels inversely related to adiposity. The *ADIPOQ* gene promoter variant −11377C>G (rs266729) has been linked to altered mRNA gene expression and obesity risk, though findings vary across populations.
**Aim:** To study the association between the *ADIPOQ* gene (−11377C>G) polymorphism and obesity, and to determine relative gene expression level of adiponectin gene mRNA expression levels in peripheral blood mononuclear cells (PBMCs) in Myanmar adult males.
**Methods:** A matched case-control study was conducted involving 114 obese (BMI ≥25 kg/m²) and 114 non-obese (BMI <25 kg/m²) adult males aged 30-60 years. Genetic analysis of *ADIPOQ* gene (−11377C>G) polymorphism was performed using PCR-RFLP method. Adiponectin mRNA expression in PBMCs was quantified in a subset of 40 individuals using SYBR Green-based qRT-PCR. SPSS v.20 was used for statistical analysis with the level of significance set at $p<0.05$.
**Results:** Genotype distributions of the *ADIPOQ* gene (−11377C>G) polymorphism obeyed to Hardy-Weinberg equilibrium. The G allele and CG genotype were significantly more common in obese subjects, with the G allele was associated with a 1.56-fold increased obesity risk (OR = 1.56, 95% CI: 1.04-2.32, p = 0.027), indicating a co-dominant effect. Mean adiponectin mRNA expression in PBMCs was 6.82-fold lower in obese compared with non-obese individuals; and there is slight increase of mRNA level in C allele carriers but not statistically significant.
**Conclusion:** The *ADIPOQ* gene (−11377C>G) polymorphism is associated with increased susceptibility to obesity in adult Myanmar males, and also, adiponectin relative gene expression level was significantly lower in obese persons, though there is no impact of SNP on adiponectin transcription in PBMCs. These findings support *ADIPOQ* as a potential genetic biomarker for obesity risk. Larger, multi-ethnic, and functionally focused studies are necessary to validate these results and to clarify gene-environment interactions in obesity pathogenesis.

**Keywords:** Obesity, *ADIPOQ* gene, *ADIPOQ* SNP -11377C>G (rs266729), PBMCs, adiponectin mRNA

## Introduction
Obesity has emerged as one of the most pressing public health challenges globally. This condition arises when energy intake chronically exceeds energy expenditure, a phenomenon increasingly prevalent due to the wide availability of energy-dense foods and sedentary lifestyles. According to the World Health Organization (WHO), obesity is defined as excessive fat accumulation in the body to the extent that it adversely affects health and well-being. The most commonly used surrogate marker for body fat content is the body mass index (BMI), calculated by dividing weight in kilograms by the square of height in meters (kg/m²). Based on BMI, the WHO classifies individuals as underweight, normal weight, overweight, or obese, with further subclassifications within obesity [1].
Obesity is associated with numerous life-threatening chronic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), and various forms of cancer. Moreover, individuals with obesity often face social stigma, discrimination, and reduced quality of life [2]. In recent decades, the global prevalence of obesity has risen dramatically, prompting the WHO to declare it a worldwide epidemic [3]. In Myanmar, the prevalence of obesity was reported to be 4.27% in men and 8.37% in women, according to Tint Swe Latt

(2011) [4]. As the country continues to undergo rapid urbanization and lifestyle changes, these figures are expected to rise.

Beyond its health implications, obesity imposes a significant financial burden on healthcare systems. The etiology of obesity is multifactorial, involving a complex interplay of environmental and genetic factors. Although lifestyle factors such as poor diet and physical inactivity are major contributors, genetic predisposition plays a significant role. To better understand the genetic basis of obesity, various approaches have been employed. Among them, the candidate gene approach focuses on identifying associations between specific genetic variants and obesity-related traits [5]. Candidate genes include those involved in adipocyte differentiation, appetite regulation, and energy homeostasis [6].

Adiponectin, a hormone predominantly secreted by adipose tissue, plays a key role in regulating glucose levels and fatty acid oxidation. It has anti-inflammatory and insulin-sensitizing properties. Unlike other adipokines, adiponectin levels are inversely correlated with body fat mass, BMI, and insulin resistance [7]. The adiponectin gene (*ADIPOQ*) is located on chromosome 3q27, spans approximately 16 kilobases, and comprises three exons. Several genome-wide linkage studies have identified this locus as being associated with obesity and metabolic syndrome traits [8].

Multiple single nucleotide polymorphisms (SNPs) in the *ADIPOQ* gene have been implicated in variations in circulating adiponectin levels, adiposity, and metabolic dysfunction [9, 10]. Among these, the promoter region SNP −11377C>G (rs266729) has received considerable attention. Several studies have linked the G allele of this SNP to decreased adiponectin levels and increased obesity risk [11-14]. Conversely, other studies have reported associations between the C allele and higher BMI or no association at all [15, 16].

Further compounding this complexity, studies have shown that both adiponectin mRNA expression in adipose tissue and circulating adiponectin levels are significantly reduced in obesity [9, 17]. Kern *et al*. (2003) demonstrated a strong correlation between plasma adiponectin levels and adipose tissue mRNA expression, with both being significantly lower in obese individuals [18]. Interestingly, sex differences also exist, with women generally having higher adiponectin levels than men, possibly due to the inhibitory effects of androgens on adiponectin production [19].

Although several SNPs in the *ADIPOQ* gene have been associated with serum adiponectin levels, few studies have explored their impact on adiponectin gene expression at the mRNA level, particularly in human subjects. Investigating gene expression in adipose tissue is methodologically challenging due to the invasive nature of tissue sampling. An alternative approach is the use of peripheral blood mononuclear cells (PBMCs), which are more easily accessible and ethically feasible. PBMCs, comprising monocytes and lymphocytes, have been shown to express adiponectin, and recent studies suggest they may serve as a surrogate model for metabolic processes occurring in adipose tissue [20, 21].

Despite the potential utility of PBMCs in metabolic research, there is a paucity of studies examining genotype-specific differences in *ADIPOQ* mRNA expression in PBMCs, particularly within the Myanmar population. Given the rising prevalence of obesity in Myanmar and the lack of data on adiponectin gene polymorphisms and expression in this population, there is a compelling need for research in this area.

By integrating genotypic and gene expression data, this study explores to provide insights into the genetic mechanisms underlying obesity and the potential role of *ADIPOQ* as a surrogate biomarker or therapeutic target. Therefore, the present study aimed to investigate the association of the *ADIPOQ* promoter variant −11377C>G (rs266729) with obesity, and to compare adiponectin mRNA expression levels in PBMCs between obese and non-obese Myanmar male population.

## Materials and Methods

This study was conducted as a case-control study to assess the association of *ADIPOQ* gene polymorphism and adiponectin gene transcription with obesity in a Myanmar male population. The research was carried out between January 2017 and December 2019 in the Mingaladon cantonment area. Laboratory analyses were performed at the Common Research Laboratory of the Defence Services Medical Academy, Yangon.

The study population comprised adult Myanmar males aged 30 to 60 years. A total of 228 subjects were recruited using a consecutive sampling method. According to the WHO criteria for Asian populations, subjects were categorized into obese (BMI ≥ 25 kg/m²) and non-obese (BMI < 25 kg/m²) groups. The minimum required sample size was calculated to be 114 individuals per group to meet the study's objectives.

Inclusion criteria for both groups included adult males aged 30-60 years. Individuals with severe illness or those receiving steroid therapy, insulin, or β-agonist medications were excluded. Written informed consent was obtained after providing a thoroughly explanation of the study objectives and procedures. Anthropometric measurements including height, weight, BMI, waist circumference, and hip circumference were conducted using standardized techniques by trained personnel. Height was measured using a wall-mounted stadiometer and weight with a calibrated digital scale, both recorded to the nearest 0.1 unit. BMI was calculated as weight (kg) divided by the square of height (m²). Waist and hip circumferences were measured using a non-stretchable tape measure, and the waist-to-hip ratio was calculated accordingly.

For genotyping, 3 mL of venous blood was collected in EDTA tubes from 114 obese and 114 non-obese participants. An additional 7 mL of blood was collected from 20 subjects in each group for gene expression analysis. Genomic DNA was extracted from leukocytes using the phenol-chloroform method. DNA purity and concentration were assessed using agarose gel electrophoresis and NanoDrop spectrophotometry. The *ADIPOQ* promoter polymorphism (−11377C>G; rs266729) was genotyped by the PCR-RFLP method using specific primers and restriction enzyme digestion with *Hha*I.

For *ADIPOQ* mRNA expression analysis, peripheral blood mononuclear cells (PBMCs) were isolated using Ficol-Paque density gradient centrifugation. Total RNA was extracted using a commercial RNA isolation kit, and its purity was assessed by measuring the A260/A280 absorbance ratio. RNA integrity was verified by gel electrophoresis. Reverse transcription and qPCR reactions were performed using a SYBR Green-based one-step RT-

PCR protocol. Gene-specific primers (QuantiTect Primer Assay, QIAGEN) were used. β-actin served as the housekeeping gene for normalization. Gene expression levels were normalized to the control group using the $2^{-\Delta\Delta CT}$ method.

Data analysis was performed using SPSS version 20. Independent t-tests and Chi-square tests were used to compare continuous and categorical variables, respectively. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess associations between SNP genotypes and obesity. A p-value of less than 0.05 was considered statistically significant. Ethical approval was obtained from the Ethical Review Committee of the Defence Services Medical Academy.

## Results

**Table 1:** General characteristics of the study population

| Variables | Obese (n = 114) (Mean ± SD) | Non-obese (n = 114) (Mean ± SD) |
|---|---|---|
| Age (years) | 41.97±8.22 | 39.01±8.36 |
| Weight (kg) | 85.46±16.75 | 58.85±6.42 |
| Height (cm) | 166.79±5.73 | 164.97±5.46 |
| BMI (kg/m$^2$) | 29.88±2.41 | 21.62 ±1.95 |
| WC (cm) | 96.02±7.21 | 73.90±4.96 |
| HC (cm) | 102.96±5.99 | 93.04±5.51 |
| WHR | 0.93±0.04 | 0.79±0.02 |
| SBP (mmHg) | 124.25±11.93 | 115.31±11.33 |
| DBP (mmHg) | 79.04±7.04 | 75.79±7.97 |
| Alcohol drinking (%) | 29 (25.4%) | 37 (32.5%) |
| Smoking (%) | 25 (21.9%) | 47 (41.2%) |

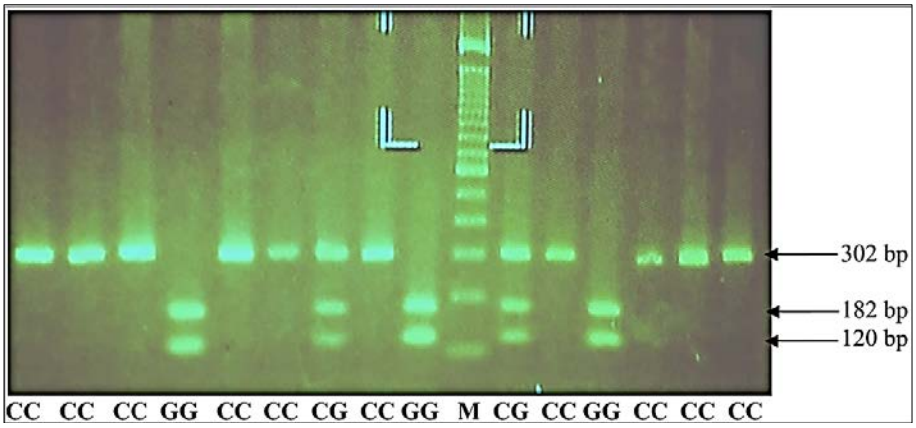


**Fig 1:** Electrophoretic analysis (2% agarose gel) of the *Hha*I polymorphism in promoter region of *ADIPOQ* gene

An example of the gel electrophoresis pattern of each genotype is presented in Figure (1). The respective genotypes are indicated above each lane. A 100 bp DNA ladder was used as the molecular weight marker. In the wild-type homozygous genotype (CC), where no *Hha*I recognition sites are present, undigested PCR products appear (lanes 1, 2, 3, 5, 6, 8, 12, 14, 15, and 16). In the mutant homozygous genotype (GG), where *Hha*I recognition sites are present, the PCR products were completely digested into two fragments of 182 bp and 120 bp, respectively (lanes 4, 9, and 13). In the heterozygous genotype (CG), three fragments appear: 302 bp, 182 bp, and 120 bp (lanes 7 and 11).

**Table 2:** Association of genotype and allele frequencies of *ADIPOQ* (-11357C>G) polymorphism with obesity

| *ADIPOQ* (-11357C>G) polymorphism | | Obesen (%) Total = 114 | Non-obese n (%) Total = 114 | Statistics | | | |
|---|---|---|---|---|---|---|---|
| | | | | $\chi^2$ | p-value | Odd Ratio (95% CI) | p-value |
| Genotypes | CC | 42 (36.84%) | 62 (54.39%) | 7.2 | 0.03 | 1 (ref) | |
| | CG | 60 (52.63%) | 42 (36.84%) | | | 2.11 (1.21 - 3.68) | 0.004 |
| | GG | 12 (10.53%) | 10 (8.78%) | | | 1.77 (0.74 - 4.53) | 0.110 |
| Alleles | C | 144 (63.16%) | 166 (72.81%) | 4.88 | 0.03 | 1 (ref) | |
| | G | 84 (36.84%) | 62 (27.19%) | | | 1.56 (1.04 - 2.32) | 0.027 |

$p$<0.05 = Significant

**Table 3:** Association of *ADIPOQ* (-11357C>G) polymorphism with obesity after adjustment for age, alcohol drinking and smoking)

| *ADIPOQ* (-11357C>G) polymorphism | Obesen (%) Total = 114 | Non-obese n (%) Total = 114 | Odd Ratio (95% CI) | p-value (adjusted for age, alcohol drinking and smoking) |
|---|---|---|---|---|
| CC | 42 (36.84%) | 62 (54.38%) | 1 (ref) | 0.020 |
| CG | 60 (52.63%) | 42 (36.84%) | 2.0 (1.12-3.60) | |
| GG | 12 (10.53%) | 10 (8.78%) | 2.22 (0.85-5.79) | 0.104 |

OR = odd ratio, C.I., = confidence interval, adjusted p<0.05 Significant

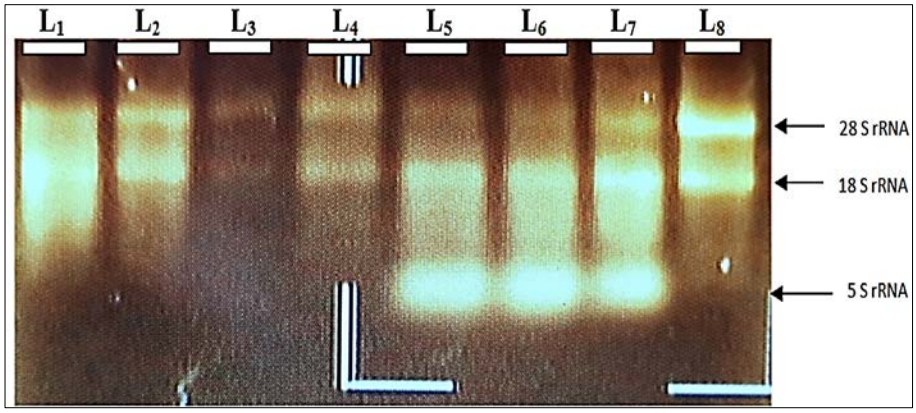


**Fig 2:** RNA integrity assessment by 1% agarose gel electrophoresis

Figure (2) shows the total RNA extraction from samples using the kit method. All lanes display distinct 18S and 28S ribosomal RNA bands, indicating intact RNA samples. A low molecular weight smear and slight degradation were observed in some samples.

**Table 4:** Comparison of relative fold change of *ADIPOQ* mRNA level between obese and non-obese (n = 40)

| | **Δ $C_T$ (Avg *ADIPOQ* $C_T$ - Avg *β-actin* $C_T$)** | **ΔΔ $C_T$ (Avg Δ$C_T$ obese - Avg Δ$C_T$ control)** | **Normalized *ADIPOQ* amount relative to control $2^{-\Delta\Delta CT}$** |
|---|---|---|---|
| Non-obese (Average) | 15.55±2.08 | 0.00±2.08 | 1.0 |
| Obese (Average) | 18.32±1.47 | 2.75 ±1.47 | -6.82 |

**Table 5:** Comparison of *ADIPOQ* mRNA expression levels in different genotypes of *ADIPOQ* (-11357C>G) (n = 40)

| **Relative gene expression** | **CC (n = 16) Mean ± SEM** | **CG + GG (n = 24) Mean ± SEM** | **Statistics** | **t-value** | **p-value** |
|---|---|---|---|---|---|
| *ADIPOQ* (Δ$C_T$) | 16.62±0.60 | 17.27±0.43 | Independent samples t-test | -0.86 | 0.395 |

## Discussion

The present study examined the relationship between the *ADIPOQ* gene promoter polymorphism −11377C>G (rs266729) and obesity, along with the adiponectin mRNA expression levels in PBMCs, among obese and non-obese adult males in the Myanmar population. Obesity is a multifactorial disorder influenced by complex interactions between genetic predisposition, environmental exposures, and lifestyle behaviors [22]. The findings of this research provide evidence that the −11377C>G variant may contribute to obesity susceptibility in this population and may influence adiponectin transcription.

The genotype distribution in this study followed to Hardy-Weinberg equilibrium, indicating that the sample was representative of the general population. The CG genotype was significantly more prevalent among obese individuals, whereas the CC genotype was more frequent in non-obese participants. The G allele was associated with a 1.56-fold higher risk of obesity, consistent with reports from several Asian and African cohorts (Table 2) [23-25]. Logistic regression analysis, adjusted for confounders such as age, alcohol consumption, and smoking, confirmed the robustness of the association, with the CG genotype conferring a two-fold increased risk of obesity (Table 4).

These findings align with the hypothesis that promoter variants in *ADIPOQ* can modulate transcription factor binding affinity, thereby altering adiponectin expression and influencing metabolic risk [26]. Prior studies in Finnish, Nigerian, and Thai populations have reported similar associations between the G allele and higher body mass index (BMI) or increased adiposity [23, 24, 27].

However, results from other populations have been inconsistent. For example, studies in Swedish and French Caucasians identified the C allele as the risk variant for obesity-related traits [15, 28], while a Han Chinese cohort reported that C allele carriers exhibited higher BMI and serum adiponectin levels than G allele carriers [29]. These "flip-flop" associations, where the risk allele differs between populations, may reflect ethnic-specific linkage disequilibrium patterns, gene-gene interactions, or environmental modifiers [30].

The *ADIPOQ* gene (−11377C>G) polymorphism was associated with significant differences in BMI and waist circumference (Table 3), phenotypic traits strongly linked to cardiometabolic risk. This association supports prior evidence that G allele carriers tend to have higher adiposity and lower plasma adiponectin levels [31-33]. Hypoadiponectinemia, characterized by reduced circulating adiponectin, is a recognized marker of metabolic dysfunction and is associated with insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular disease [34].

This study further explored the functional consequences of the *ADIPOQ* gene (−11377C>G) polymorphism by quantifying *ADIPOQ* mRNA levels in PBMCs. On average, adiponectin expression was 6.82-fold higher in the non-obese group than in the obese group, consistent with the established inverse relationship between adiponectin levels and obesity (Table 5) [35, 36]. The −11377C>G variant lies in the promoter region of *ADIPOQ* gene, potentially altering transcriptional regulation. Variants in this region may disrupt transcription factor binding, leading to reduced gene expression and, consequently, lower circulating adiponectin [37].

Interestingly, while obese individuals carrying the G allele (CG + GG genotype) exhibited lower mean adiponectin mRNA levels than C allele (CC genotype) carriers, the genotype-specific difference was not statistically significant (Table 6). This lack of significance may reflect the relatively

small sample size (n = 40) for expression analysis, limiting statistical power. Additionally, PBMCs, though a convenient source for RNA profiling, are not the primary site of adiponectin synthesis; expression patterns in adipose tissue may more accurately represent functional effects [38].

Multiple studies have linked rs266729 with both reduced adiponectin levels and higher metabolic risk. Divella *et al*. (2017) observed that G allele carriers had significantly lower plasma adiponectin compared to C allele carriers [39], and Tankó *et al*. (2005) demonstrated a similar pattern in postmenopausal women [40]. Mechanistically, reduced adiponectin impairs fatty acid oxidation and glucose utilization, promoting adipose accumulation and insulin resistance [9]. These functional observations provide a plausible biological pathway linking the −11377C>G polymorphism to obesity.

Conversely, some populations have not demonstrated such functional effects. Hivert *et al*. (2008) in the Framingham Offspring Study found no association between *ADIPOQ* variants and BMI, waist circumference, or visceral fat volume [41]. Such discrepancies may be explained by differences in study design, sample size, ethnic background, and environmental influences.

The phenotypic impact of *ADIPOQ* variants may be modulated by environmental and epigenetic factors. DNA methylation of the *ADIPOQ* promoter and histone modifications can alter transcriptional activity in response to dietary patterns, physical activity, and obesity status [42, 43]. In addition, lifestyle interventions such as caloric restriction and exercise have been shown to increase adiponectin expression independently of genetic variation [44]. Thus, differences in diet, physical activity, and other lifestyle factors between populations could partly explain the heterogeneity in reported associations.

Several limitations should be acknowledged. First, the study focused exclusively on adult males to reduce sex hormone-related confounding, as estrogen is known to upregulate adiponectin expression [45]. However, this selection limits the generalizability of the findings to females. Second, the cross-sectional design prevents causal inference regarding whether the G allele predisposes individuals to obesity or whether obesity-related metabolic changes influence gene expression. Longitudinal studies are needed to clarify temporal relationships.

Third, although PBMCs are accessible for gene expression studies, they may not fully capture adiponectin transcriptional regulation occurring in adipose tissue. Future research incorporating adipose biopsies could provide more direct insights. Fourth, lifestyle factors such as diet and physical activity, which were not comprehensively assessed in this study, may act as important confounders or effect modifiers.

Despite these limitations, the integration of genetic association data with mRNA expression profiling represents a methodological strength. By linking a functional promoter polymorphism to both obesity risk and altered adiponectin expression, this study provides a more comprehensive understanding of how genetic variation may contribute to obesity pathogenesis in the Myanmar population.

The *ADIPOQ* gene (−11377C>G) variant may have potential as a predictive genetic marker for obesity risk. If validated in larger, multiethnic cohorts, this information could be incorporated into personalized risk assessment tools, enabling targeted prevention strategies for individuals genetically predisposed to obesity. Furthermore, since adiponectin plays a key role in insulin sensitivity and lipid metabolism, interventions that increase adiponectin expression such as lifestyle modification, pharmacological agents (e.g., thiazolidinediones), or dietary supplementation may be particularly beneficial for G allele carriers.

## Conclusion

The *ADIPOQ* −11377C>G (rs266729) promoter polymorphism is significantly associated with obesity risk in adult Myanmar males, with G allele carriers showing a 1.56-fold higher susceptibility. Obese individuals had markedly lower adiponectin mRNA expression in PBMCs, supporting their use as a surrogate tissue for gene expression studies, although expression differences by genotype were not significant. These results are consistent with many Asian and African studies but differ from some Caucasian findings, emphasizing the need for population-specific research. Given the modest sample size, further studies with larger, more diverse cohorts, multi-SNP analyses, and exploration of gene environment interactions are required. Such work will help clarify the genetic basis of obesity and guide precision medicine strategies in the Myanmar population.

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## References

1. World Health Organization. *Obesity: preventing and managing the global epidemic: report of a WHO consultation*. Geneva: World Health Organization; 2000. p. 1-253.
2. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, *et al*. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. Jama. 2003;289(1):76-79.
3. NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature. 2019;569(7755):260-264.
4. Latt TS, Ko K, Aye TT, Thidar A, Khin EE. A summary of the Myanmar clinical practice guidelines for the management of obesity. J ASEAN Fed Endocr Soc. 2011;26(2):105-105.
5. Cheung WW, Mao P. Recent advances in obesity: genetics and beyond. Int Sch Res Not. 2012;2012:1-12.
6. Bell CG, Walley AJ, Froguel P. The genetics of human obesity. Nat Rev Genet. 2005;6(3):221-234.
7. Ukkola O, Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities? J Mol Med. 2002;80(11):696-702.
8. Ling H, Waterworth DM, Stirnadel HA, Pollin TI, Barter PJ, Kesäniemi YA, *et al*. Genome-wide linkage and association analyses to identify genes influencing

adiponectin levels: the GEMS Study. Obesity. 2009;17(4):737-744.
9. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, *et al*. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med. 2001;7(8):941-946.
10. Nedvidkova J, Smitka K, Kopsky V, Hainer V. Adiponectin, an adipocyte-derived protein. Physiol Res. 2005;54(2):133-140.
11. Vasseur F, Helbecque N, Lobbens S, Vasseur-Delannoy V, Dina C, Clement K, *et al*. Hypoadiponectinaemia and high risk of type 2 diabetes are associated with adiponectin-encoding (ACDC) gene promoter variants in morbid obesity: evidence for a role of ACDC in diabesity. Diabetologia. 2005;48(5):892-899.
12. Hoefle G, Muendlein A, Saely CH, Risch L, Rein P, Koch L, *et al*. The -11377 C> G promoter variant of the adiponectin gene, prevalence of coronary atherosclerosis, and incidence of vascular events in men. Thromb Haemost. 2007;97(3):451-457.
13. Kaklamani VG, Wisinski KB, Sadim M, Gulden C, Do A, Offit K, *et al*. Variants of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes and colorectal cancer risk. Jama. 2008;300(13):1523-1531.
14. Ong KL, Li M, Tso AW, Xu A, Cherny SS, Sham PC, *et al*. Association of genetic variants in the adiponectin gene with adiponectin level and hypertension in Hong Kong Chinese. Eur J Endocrinol. 2010;163(2):251-257.
15. Gu HF, Abulaiti A, Östenson CG, Humphreys K, Wahlestedt C, Brookes AJ, *et al*. Single nucleotide polymorphisms in the proximal promoter region of the adiponectin (APM1) gene are associated with type 2 diabetes in Swedish caucasians. Diabetes. 2004;53(Suppl 1):S31-S35.
16. Hsiao TJ, Lin E. A validation study of adiponectin rs266729 gene variant with type 2 diabetes, obesity, and metabolic phenotypes in a Taiwanese population. Biochem Genet. 2016;54(6):830-841.
17. Hu E, Liang P, Spiegelman BM. *AdipoQ* is a novel adipose-specific gene dysregulated in obesity (*). J Biol Chem. 1996;271(18):10697-10703.
18. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-α expression. Diabetes. 2003;52(7):1779-1785.
19. Renaldi O, Pramono B, Sinorita H, Purnomo LB, Asdie RH, Asdie AH. Hypoadiponectinemia: a risk factor for metabolic syndrome. Acta Med Indones. 2009;41(1):20-24.
20. Crawford LJ, Peake R, Price S, Morris TC, Irvine AE. Adiponectin is produced by lymphocytes and is a negative regulator of granulopoiesis. J Leukoc Biol. 2010;88(4):807-811.
21. Bouwens M, Afman LA, Müller M. Fasting induces changes in peripheral blood mononuclear cell gene expression profiles related to increases in fatty acid β-oxidation: functional role of peroxisome proliferator-activated receptor α in human peripheral blood mononuclear cells. Am J Clin Nutr. 2007;86(5):1515-1523.
22. Hruby A, Hu FB. The epidemiology of obesity: a big picture. Pharmacoeconomics. 2015;33(7):673-689.
23. Ogundele OE, Adekoya KO, Osinubi AA, Awofala AA, Oboh BO. Association of adiponectin gene (ADIPOQ) polymorphisms with measures of obesity in Nigerian young adults. Egypt J Med Hum Genet. 2018;19(2):123-127.
24. Siitonen N, Pulkkinen L, Lindström J, Kolehmainen M, Eriksson JG, Venojärvi M, *et al*. Association of ADIPOQ gene variants with body weight, type 2 diabetes and serum adiponectin concentrations: the Finnish Diabetes Prevention Study. BMC Med Genet. 2011;12(1):5.
25. Suriyaprom K, Phonrat B, Tungtrongchitr R. Association of adiponectin gene -11377C>G polymorphism with adiponectin levels and the metabolic syndrome in Thais. Asia Pac J Clin Nutr. 2014;23(1):167-173.
26. Menzaghi C, Ercolino T, Salvemini L, Coco A, Kim SH, Fini G, *et al*. Multigenic control of serum adiponectin levels: evidence for a role of the APM1 gene and a locus on 14q13. Physiol Genomics. 2004;19(2):170-174.
27. Lu J-fu, Zhou Y, Huang G-hua, Jiang H-xing, Hu B-li, Qin S-yu. Association of ADIPOQ polymorphisms with obesity risk: a meta-analysis. Hum Immunol. 2014;75(10):1062-1068.
28. Bouatia-Naji N, Meyre D, Lobbens S, Séron K, Fumeron F, Balkau B, *et al*. ACDC/adiponectin polymorphisms are associated with severe childhood and adult obesity. Diabetes. 2006;55(2):545-550.
29. Du J, Ye X-hua, Li Q, Yu X, Cheng J, Ma J, *et al*. Genetic variants in the ADIPOQ gene and the risk of metabolic syndrome: a case-control study of a Chinese Han population. Ann Hum Genet. 2012;76(2):101-109.
30. Lin PI, Vance JM, Pericak-Vance MA, Martin ER. No gene is an island: the flip-flop phenomenon. Am J Hum Genet. 2007;80(3):531-538.
31. Divella R, Daniele A, Mazzocca A, Abbate I, Casamassima P, Caliandro C, *et al*. ADIPOQ rs266729 G/C gene polymorphism and plasmatic adipocytokines connect metabolic syndrome to colorectal cancer. J Cancer. 2017;8(6):1000-1007.
32. Khan MM, Sonkar GK, Alam R, Singh S, Mehrotra S, Sonkar SK. Association of ADIPOQ gene variant rs266729 with circulatory adiponectin levels in patients with type 2 diabetes in North Indian population: a case-control study. Biomed Pharmacol J. 2017;10(1):407-417.
33. Tankó LB, Siddiq A, Lecoeur C, Larsen PJ, Christiansen C, Walley A, *et al*. ACDC/adiponectin and PPAR-γ gene polymorphisms: implications for features of obesity. Obes Res. 2005;13(12):2113-2121.
34. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116(7):1784-1792.
35. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J-ichiro, *et al*. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. 1999;257(1):79-83.
36. Matsuzawa Y. Adiponectin: identification, physiology and clinical relevance in metabolic and vascular disease. Atheroscler Suppl. 2005;6(2):7-14.
37. Mojtaba E, Taghi GM, Davood K, Houssein D, Hamidreza S. Relationship of serum adiponectin and

beta-cell function in obese males with type 2 diabetes. Asian J Pharm Biol Res AJPBR. 2012;2(1):1-6.
38. Kondo H, Shimomura I, Matsukawa Y, Kumada M, Takahashi M, Matsuda M, *et al*. Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome. Diabetes. 2002;51(7):2325-2328.
39. Divella R, De Luca R, Abbate I, Naglieri E, Daniele A. Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation. J Cancer. 2016;7(15):2346-2359.
40. Tankó LB, Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. Circulation. 2005;111(15):1883-1890.
41. Hivert MF, Manning AK, McAteer JB, Florez JC, Dupuis J, Fox CS, *et al*. Common variants in the adiponectin gene (ADIPOQ) associated with plasma adiponectin levels, type 2 diabetes, and diabetes-related quantitative traits: the Framingham Offspring Study. Diabetes. 2008;57(12):3353-3359.
42. Borgel J, Guibert S, Li Y, Chiba H, Schübeler D, Sasaki H, *et al*. Targets and dynamics of promoter DNA methylation during early mouse development. Nat Genet. 2010;42(12):1093-1100.
43. Kim AY, Park YJ, Pan X, Shin KC, Kwak SH, Bassas AF, *et al*. Obesity-induced DNA hypermethylation of the adiponectin gene mediates insulin resistance. Nat Commun. 2015;6(1):1-11.
44. Simpson KA, Singh MAF. Effects of exercise on adiponectin: a systematic review. Obesity. 2008;16(2):241-256.
45. Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, *et al*. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes. 2002;51(9):2734-2741.