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Association of Genotypes and Alleles of Adiponectin Gene in Type 2 Diabetes Mellitus: A Cross-Sectional Analysis

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Abstract

***Objective*:** The aim of the study was to find out the association between genotypes as well as the allele frequencies of *ADIPOQ* (Adiponectin gene) and its predisposition to Type 2 Diabetes Mellitus (T2DM), by comparing affected individuals with non-diabetic controls.

***Methodology*:** The study was conducted at Ziauddin University Hospital, Karachi, over the period from January 2018 - 20. A cohort of participants (200) was recruited, comprising 100 patients diagnosed with T2DM and 100 age-matched non-diabetic controls, aged between 25 and 65 years. Following informed consent, relevant demographic information, medical history, and associated risk factors were meticulously documented. PCR was used to determine the Genotypic and allelic distributions of the *ADIPOQ* gene. SmaI restriction enzyme was used for RFLP analysis. Data was analyzed using SPSS ver 21.

***Results*:** Within the diabetic cohort, 67% exhibited the TT genotype, as opposed to 79% in the control group, statistically it was not significant (p=0.16). Nevertheless, a significant divergence was observed in allele frequencies: the T allele was present in 81% of diabetics compared to 89% of controls, whereas, 19% of diabetics and 11% of controls had G ($p<0.05$). Occurrence of allele G in the diabetic group was notably higher. The odds ratio calculated for the T allele was 0.581(95% CI:0.334–1.011), whereas, for G allele it was 1.72 (95% CI: 0.988–2.99).

***Conclusion*:** The allele T of Adiponectin gene may confer a protecting effect for non-diabetic individuals, however, allele G showed association with an increase in risk of developing T2DM. Future researches with larger and more diverse cohorts, be undertaken to substantiate these observations.

Keywords: Genetic polymorphism, restriction fragment length polymorphism (RFLP), adiponectin gene, type 2 diabetes mellitus.

1. INTRODUCTION

Adiponectin, synthesized by adipose tissue, is a hormone which exists in various isoforms, AdipoQ, Acrp30, and APM1, however, the precise roles of these multimers remain poorly understood. Well-known for its anti-atherosclerotic, anti-diabetic, and anti-inflammatory, functions, adiponectin also plays a pivotal role in the homeostasis of glucose by enhancing glucose uptake in skeletal muscle during the post-absorptive phase. Low adiponectin levels are associated strongly with an increased risk of T2DM, while higher concentrations are linked to improved insulin sensitivity, likely driven by enhanced fatty acid oxidation via activation of AMPK the AMP-activated protein kinase. Paradoxically, despite increased adipose tissue in obesity, circulating adiponectin levels are often reduced, underscoring the complex and nuanced relationship between adiponectin and metabolic health. [1].

Among the various genetic factors influencing glucose metabolism, the *ADIPOQ* gene holds particular significance. Located on chromosome 3q27, this gene is of interest due to its strong linkage to both T2DM and obesity. Spanning approximately 17 kilobases, the *ADIPOQ* gene encodes a 244-amino acid protein, adiponectin. The gene consists of 2 introns, and 3 exons, secreted exclusively by white adipose tissue. Structurally, adiponectin comprises a short N-terminal variable region, collagen-like repeats, and a large C-terminal globular

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domain—an intricate structure essential for its role in maintaining metabolic balance, regulating glucose levels, and promoting lipid catabolism. Notably, several SNPs (single nucleotide polymorphism) within *ADIPOQ* gene have association with metabolic disorders, including insulin resistance, obesity, as well as T2DM [2].

Genetic mutations that impair the multimerisation of adiponectin are believed to contribute to the pathogenesis of diabetes. Certain mutations hinder the formation of high-molecular-weight adiponectin, whilst others impede trimer assembly, thereby reducing adiponectin secretion. Insulin resistance, characterised by a diminished cellular response to insulin, is further aggravated by the secretion of various adipokines from adipose tissue, including leptin, plasminogen activator inhibitor-1, resistin, TNF-α and angiotensinogen [3].

Thymine-to-guanine substitution at position +45 (rs2241766) in exon 2, is the most extensively studied SNPs within the *ADIPOQ* gene. It has been linked to metabolic syndrome dyslipidemia, glucose intolerance, insulin resistance and various other metabolic abnormalities [4].

Furthermore, the *ADIPOQ* gene, which encodes adiponectin, plays a crucial role in regulating insulin sensitivity and is implicated in the risk of developing Type 2 Diabetes Mellitus (T2DM). Polymorphisms in the *ADIPOQ* gene can significantly affect adiponectin levels, insulin resistance, and consequently, T2DM risk. Variants of *ADIPOQ* gene such as rs266729 and rs1501299 have been associated with altered adiponectin levels, impacting insulin sensitivity. [5]. Lower adiponectin levels correlate with higher insulin resistance, suggesting that these polymorphisms may hinder adiponectin's insulin-sensitizing effects [6].

Studies on individuals with Insulin Resistance and T2DM Risk indicate that such individuals with specific *ADIPOQ* polymorphisms exhibit higher insulin resistance, which is a precursor to T2DM [6]. For instance, the GG genotype of rs17300539 is linked to increased insulin resistance and a higher prevalence of metabolic syndrome [7].

Research in diverse populations, including the Kazakh and Indonesian groups, shows significant associations between *ADIPOQ* polymorphisms and T2DM risk, emphasizing the genetic component in different ethnic backgrounds [5, 8]. Conversely, while certain polymorphisms are linked to increased T2DM risk, not all studies find significant associations, indicating the complexity of genetic influences on diabetes and the need for further research to clarify these relationships [8].

Despite its recognized significance, research on the distribution and impact of adiponectin gene variants within the population of Pakistan remains scarce. This study aims to bridge this knowledge gap by examining the genotypes and frequency of alleles of ADIPOQ in individuals with Type 2 Diabetes Mellitus (T2DM) and comparing them to non-diabetic controls.

2. METHODOLOGY

Consecutive sampling technique was used for sample collection. Sample size was calculated using Epi info software adding hypothetical proportion of cases with exposure were 16.98% (Aamir A.H *et al*. 2018) 90% power and 95% confidence interval) [9]. It was calculated and 200 subjects (100 controls and 100 cases) were confirmed for the study. The study design was cross-sectional.

From the peripheral blood samples, Genomic DNA was extracted using the QIAGEN DNA extraction kit, according to the protocol of the manufacturer. The purity and concentration of isolated DNA were assessed with a Nanodrop spectrophotometer by measuring the 260/280 nm absorbance ratio. To verify the integrity of the extracted DNA, samples were analyzed using agarose gel electrophoresis. The purified DNA was subsequently stored at 4°C until further analysis via Polymerase Chain Reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) techniques.

PCR was carried on a 25 µL reaction mixture, composed of the following constituents of the master mix:

- 4.5 µL of DNA
- 2 µL of both forward (F) and reverse (R) primers:
  - F: 5′-GAAGTAGACTCTGCTGAGATGG-3′
  - R: 5′-TATCAGTGTAGGAGGTCTGTGATG-3′
- Rest of ingredients were dNTPs, $MgCl_2$, PCR buffer and Taq DNA polymerase
- 4 µL of nuclease-free water

The amplification specifically targeted exon 2 (+45, codon 15) of the ADIPOQ gene, encompassing the T/G (rs2241766) polymorphism.

The PCR cycling protocol was:

- Initial denaturation: 96°C for 3 minutes
- Followed by 30 cycles of:
  - Denaturation at 94°C for 30 seconds
  - Annealing at 60°C for 30 seconds
  - Extension at 72°C for 30 seconds
- Final extension at 72°C for 7 minutes

To ensure experimental integrity and prevent contamination, both positive and negative controls were incorporated into every PCR run.

RFLP: the amplified products of PCR were further evaluated by RFLP. 1.0 unit of the *SmaI*, the restriction enzyme and PCR product was incubated at 30°C for 4 hours to ensure complete enzymatic digestion. To visualize the DNA fragments, the digested mixture (5 µL) was observed on 2% agarose gel with 0.5 µg/mL of ethidium bromide. The separated fragments were then examined under UV transillumination, with their sizes compared against a 100 bp DNA ladder.

The restriction digestion patterns were interpreted as follows:

- Allele G: Two distinct bands of 318 bp and 148 bp
- Allele T: A single band of 466 bp

The data, Clinical and biological, were presented as percentages or mean ± standard deviation (SD), as appropriate. Comparative analysis between T2DM patients and control subjects was conducted using either an unpaired Student's t-test or the Chi-square test, depending on the nature of the data. A one-way ANOVA was utilised to compare values across three groups.

To evaluate whether the genotype distributions in the control group conformed to Hardy-Weinberg equilibrium (HWE), a Chi-square test was performed. The odds ratios (ORs) with 95% confidence intervals (CIs) was used to assess association between genotypes and T2DM risk. Data was analyzed using SPSS ver 21. Descriptive data was compared in different groups by one-way analysis of variance (ANOVA) test, p-value <0.05 was considered significant, following adjustments for multiple comparisons.

3. RESULTS

The study finalized 100 diabetics and 100 healthy controls. The age ranged between 25–65 years (mean age 52.3 ± 9.6 years). The BMI ($p = 0.119$) and age ($p = 0.131$) were not found significantly different between the two groups, however, weight ($p = 0.013$) and height ($p = 0.01$) showed significant results, that is higher in diabetics than controls (Table **1**).

Triglycerides, total cholesterol, LDL, HbA1C as well as FBS, were found significantly raised in diabetics ($p < 0.001$ for all parameters), compared to controls, reinforcing well-established metabolic disturbances associated with diabetes.

Body Mass Index (BMI) was generally high in individuals with diabetes comparing to non-diabetic individuals. Within the control group, females exhibited a higher BMI than their male counterparts, whereas in the diabetic cohort, males demonstrated a greater BMI. In a similar way, weight, waist circumference, and hip circumference were all had significant elevation in diabetics.

Table 1: Demographic and clinical parameters of study participants.

Variable	Controls (Mean ± SD)	Diabetics (Mean ± SD)	p-value
Age (years)	52.3 ± 9.6	51.9 ± 9.2	0.131
BMI (kg/m²)	25.3 ± 5.1	27.8 ± 6.2	0.119
Height (cm)	161.2 ± 6.8	164.1 ± 7.3	**0.01**
Weight (kg)	66.5 ± 12.4	73.2 ± 9.6	**0.013**
Waist Circumference (cm)	88.3 ± 5.8	98.2 ± 4.7	**<0.001**
Hip Circumference (cm)	94.2 ± 5.2	101.6 ± 3.9	**<0.001**
Waist-Hip Ratio	0.94 ± 0.05	1.00 ± 0.04	**<0.001**

Table 2: The Genotype and Allele frequencies of *ADIPOQ SNP45* gene in diabetics and controls.

Genotype	Diabetics (N=100)	Controls (N=100)	p-value
TT	67 (67%)	79 (79%)	0.16
TG	28 (28%)	18 (18%)	
GG	5 (5%)	3 (3%)	
T allele (%)	162 (81%)	178 (89%)	**<0.05**
G allele (%)	38 (19%)	22 (11%)	

When considering both groups collectively, males consistently displayed higher values for weight and body measurements, highlighting gender-based disparities in body composition. These findings underscore the influence of sex-specificphysiological differences on anthropometric characteristics.

The genotypic distribution of *ADIPOQ* SNP45 did not reveal a statistically significant difference between the diabetic group and control group ($p = 0.16$). However, a significant divergence was noted in the allelic distribution ($p < 0.05$). Specifically, was more prevalent among controls (89%) compared to diabetics (81%), suggesting T allele as potentially protective allele against T2DM, see Table **2**.

There was higher frequency of T allele in non diabetics, reinforcing its possible protective function, while the G allele was more common in diabetics, suggesting an association with increased diabetes susceptibility. The odds ratio for the T allele was 0.581 (95% CI: 0.334–1.011), whereas for the G allele, it was 1.72 (95% CI: 0.988–2.99), further supporting these trends.

When diabetic participants were further categorized into obese and non-obese subgroups, the genotypic distribution remained statistically non-significant ($p = 0.387$). The frequency, however, of the protective "T" allele decreased in obese diabetics compared to non-obese diabetics, while the risk-associated G allele was higher in obese diabetics (Table **3**).

While genotype distributions did not reach statistical significance, the T allele frequency declined from 89% in controls to 82% in obese diabetics and 79% in non-obese diabetics, strengthening the hypothesis of its protective role. Conversely, the G allele frequency increased in diabetic groups, particularly among the obese subgroup (18%), further suggesting a link between G allele presence and diabetes risk.

PCR-RFLP analysis of *ADIPOQ* SNP45 revealed distinct banding patterns for the TT (wild type), GG (homozygous mutant), and TG (heterozygous) genotypes, as depicted in Fig. (**1**).

Table 3: Genotypic and allelic frequencies of *ADIPOQ* SNP45 in obese and non-obese diabetics.

Genotype	Controls (N=100)	Non-Obese Diabetics (N=38)	Obese Diabetics (N=62)	p-value
TT	79 (79%)	24 (63%)	43 (69%)	0.387
TG	18 (18%)	12 (32%)	16 (26%)	
GG	3 (3%)	2 (5%)	3 (5%)	
T allele (%)	178 (89%)	60 (79%)	102 (82%)	0.126
G allele (%)	22 (11%)	16 (21%)	22 (18%)	

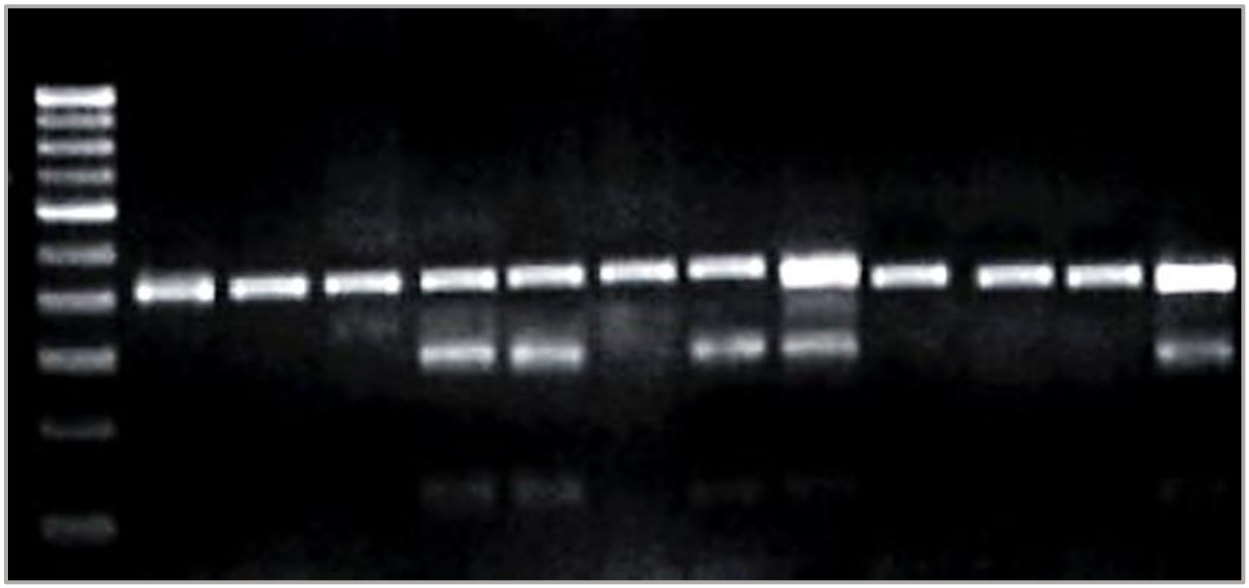

Figure 1: PCR-RFLP Electrophoresis of *ADIPOQ SNP45*. TT (wild type), GG (mutant), and TG (heterozygous) genotypes).

4. DISCUSSION

The association between the adiponectin gene and Type 2 Diabetes Mellitus (T2DM) and has been the subject of extensive investigation, with various genetic polymorphisms identified as potential contributors to the disease. Ramya *et al*. [10] observed significant association between specific genotypes of *ADIPOQ* gene with T2DM, obesity, and hypoadiponectinaemia within a South Indian population. The locus on chromosome 3q27, locates the *ADIPOQ* gene, this locus is linked to metabolic syndrome and T2DM, thereby reinforcing its role in diabetes susceptibility. In a study conducted by Rabia Farooq [11] among the Kashmiri population, the findings were consistent with those of other investigations, revealing that high level of adiponectin correlates with a low risk of developing diabetes across populations in Japan, Mexico, Asia, and Kashmir.

Within the Vitamin D Receptor (VDR) gene, the FokI polymorphism was examined. It was observed in both the case and control groups, it conforms to Hardy-Weinberg equilibrium ($p > 0.05$), whereas other variants, such as Apa I and Taq I, did not exhibit this equilibrium. For the adiponectin gene, equilibrium was maintained within the diabetic group, whilst the Ras gene demonstrated equilibrium within the control cohort. These findings may be attributable to the genetic heterogeneity of the population of Karachi, a characteristic similarly noted in other population studies [12].

Several single nucleotide polymorphisms (SNPs) within genes such as APM1, IGF2BP2, CAPN10, and FUT6 were found connected to an more exposure to T2DM in populations of Uyghur and Han Chinese descent. In the Tahe populations of Japan and China, SNPs +45 and +276 in the adiponectin gene were associated with a greater risk of T2DM, predominantly among individuals carrying the GG genotype at either SNP+45 or SNP+276. Conversely, a study by Wang *et al*. [13] in southwest China's Yi and Han populations showed no statistically significant associations among SNP+45 variant and T2DM ($p > 0.05$). Additionally, no link was identified between SNP+45T>G and insulin resistance within populations from Italy, France, and Sweden, suggesting that genetic variability may account for these differences.

In contrast, while SNP+276 was not significantly linked to T2DM in populations from Hans China and Iran, SNP+45 was found to be associated within these cohorts [4]. In the present investigation, conducted among a Filipino population [14], no significant differences were observed in adiponectin levels among individuals with different T45G SNP genotypes. Although research among Chinese and Malaysian populations has linked the TG+GG genotype to lower adiponectin levels, studies involving Arab, Bulgarian, and Iranian populations have not corroborated this association. Such inconsistencies imply that the impact of the TG+GG genotype on adiponectin concentrations and diabetes risk may be contingent upon population-specific genetic or environmental factors. In a study by Li Z [15], T2DM within the Chinese population was closely linked to *ADIPOQ* gene variants rs1501299, rs182052, and rs7627128, corroborating earlier findings among Chinese diabetic nephropathy patients [16, 17].

The results of the present study lend further support to these observations, demonstrating a strong association between adiponectin gene polymorphisms and T2DM. The TG/GG genotype was markedly more prevalent in diabetics (36.7%) in comparison to non-diabetics (18%), with the G/G genotype exhibiting an even stronger correlation with the disease. These results are in accordance with one of the meta-analysis that identified the *ADIPOQ* +276 G > T polymorphism as a risk factor for diabetes, particularly among men of European descent [18]. Similarly, the rs266729 polymorphism has been shown to increase the likelihood of T2DM [19]. Further studies have identified adiponectin gene variants as risk factors across diverse populations, including those in Kazakhstan [20] and overweight individuals in Europe [21]. Collectively, these findings underscore the notion that adiponectin gene polymorphisms are pivotal in influencing T2DM susceptibility.

The present findings are consistent with other investigations exploring the relationship between adiponectin gene variants and T2DM, including those by Hara *et al*. [22] in Japan, Alimi *et al*. [23] in Europe, and Fumeron *et al*. [24] in France. Additionally, the occurrence of the G allele within GG and TG haplotypes has been linked to a 3.79-fold increase in T2DM risk [25], a result consistent with findings by others mentioned above.

From a broader perspective, the influence of the adiponectin gene on T2DM may stem from its direct effects on insulin sensitivity and its interaction with other genetic and environmental determinants [26]. Moreover, variations in adiponectin have been implicated in the increased risk of cardiovascular disease among individuals suffering from T2DM.

Although the researches are in accordance with those of other investigations [18, 23, 27], it is essential to acknowledge the variability in results across populations. These discrepancies may be attributed to backgrounds, with different genetics, lifestyle factors, and exposures to environment, all of which may modulate the effect of adiponectin gene variants on T2DM risk. In light of the multifactorial nature of T2DM, future studies with more diverse and larger sample sizes is necessary to elucidate the role of adiponectin gene polymorphisms in disease pathogenesis.

Research in different populations indicates that *ADIPOQ* polymorphisms are significantly associated with Type 2 Diabetes Mellitus (T2DM) risk in diverse populations, including Kazakh and Indonesian groups. These genetic variations highlight the importance of ethnicity in understanding diabetes susceptibility. However, not all studies consistently find these associations, underscoring the complexity of genetic influences on T2DM.

Genetic Associations in Kazakh Population shows significant associations between ADIPOQ gene polymorphisms and T2DM, particularly with rs266729, which correlates with obesity and fasting glucose levels [5]. Other polymorphisms, such as those in TCF7L2 and KCNQ1, also demonstrate links to metabolic indicators in this group [28].

Genetic studies regarding variability across ethnic groups reveal that certain polymorphisms may have different impacts across ethnicities, with East Asian populations exhibiting unique genetic clusters associated with T2DM [29]. The complexity of T2DM genetics is further illustrated by the varying results across studies, suggesting that environmental factors and lifestyle may interact with genetic predispositions [5, 29]. While genetic factors play a crucial role in T2DM risk, the inconsistent findings across studies highlight the need for further research to clarify these relationships and consider environmental influences. This complexity suggests that a multifaceted approach is essential for understanding T2DM across diverse populations.

This study strengthens the expanding body of evidence linking adiponectin gene variants, particularly the SNP+45 and SNP+276 variants, with an increased risk of T2DM. While these findings are consistent with numerous studies conducted across diverse populations, additional research is essential to unravel the precise molecular mechanisms underlying these associations. Furthermore, exploring the potential role of adiponectin gene variations could offer valuable insights into developing targeted strategies for the prevention and management of T2DM.

In our study within the diabetic cohort, 67% exhibited the TT genotype, as opposed to 79% in the control group, statistically it was not significant ($p=0.16$). Nevertheless, a significant divergence was observed in allele frequencies: the T allele was present in 81% of diabetics compared to 89% of controls, whereas, 19% of diabetics and 11% of controls had G ($p<0.05$).

The discrepancy between genotypic and allelic distributions can arise from several underlying factors, including population structure, methodological biases, and genetic drift. Understanding these factors is crucial for interpreting genetic data accurately in a population structure. Different populations, due to ethnic variations, may exhibit distinct allele frequencies due to historical migration and selection pressures, which can lead to discrepancies in observed genotypes and alleles [30]. Ouali *et al*. 2024, [30], also observed athletes may exhibit variation in genotypic distribution between cyclists and hockey players suggesting sport-specific selection may influence allele frequencies, reflecting adaptations to different physical demands. Some researchers also suggest that in small populations, due to random Fluctuations a genetic drift can lead to significant

differences in allele frequencies over generations, contributing to discrepancies in genotypic distributions [31].

While these factors can explain discrepancies, it is also important to consider that some variations may not be biologically significant and could arise from sampling errors or methodological limitations. Understanding these nuances is essential for accurate genetic analysis.

5. CONCLUSION

The adiponectin gene polymorphism is associated with reduced susceptibility to type 2 diabetes mellitus in the Karachi population, with a significant p-value and an odds ratio (OR) greater than 1 for the G allele in controls and less than 1 for the *T* allele in diabetics. However, no significant difference was observed when comparing this polymorphism among controls, obese diabetics, and non-obese diabetics, indicating that adiponectin gene polymorphism poses a lower risk for type 2 diabetes mellitus.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest to disclose.

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