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Original Article

Association of rs2910164, rs57095329 polymorphisms in miR146a and rs11614913 polymorphisms in miR196a2 with susceptibility to type 2 diabetes

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Abstract

Background and Aim: Studies have confirmed the significance of microRNAs (miRNAs) in various biological processes. Various miRNAs have been studied in diabetes mellitus, among them miR-146a and miR-196a2 play an important role in the development of this disease. This research aims to examine the frequency of rs2910164, rs57095329 polymorphisms in miR-146a and rs11614913 in miR-196a2, T2DM patient comparing to control group.

Methods: One hundred patients with T2DM and 100 healthy individuals as normal control group were included in this study. Polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) was exploited for genotyping of rs2910164C>G and rs11614913C>T and amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) was used for rs57095329A>G. Genotypes frequencies were evaluated with chi square test.

Results: We found that the GG genotype rs2910164 is significantly associated with T2DM susceptibility (OR = 12.1, 95% CI = 1.36-7.9, P = 0.003). Another investigation showed a significant association between the TT genotype of rs11614913 polymorphism and T2DM susceptibility (OR = 4.36, 95% CI = 1.13-5.84, P = 0.006). The GG genotype of rs57095329 showed a significant difference between T2DM and controls (OR = 8.37, 95% CI = 3.07 - 22.82, P < 0.0001).

Conclusion: To sum up, the study found that three genetic variants, rs2910164C>G, rs11614913C>T, and rs57095329A>G, were associated with an increased risk of type 2 diabetes mellitus (T2DM) in the Iranian population. These findings suggest that these variants may be new risk factors in the development of T2DM.

Keywords: type 2 diabetes, polymorphism, miR146a, miR196a2

1. Introduction

Diabetes is a metabolic disorder that elevates glucose levels in the bloodstream, leading to damage to the heart, blood vessels, eyes, kidneys, and nerves (1). There are two types of diabetes: Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). T1DM is an autoimmune disorder in which immune cells attack and destroy β-cells in the pancreas responsible for insulin production, while T2DM is caused by a gradual impairment in insulin secretion and the development of insulin resistance (2). The majority of cases (over 90%) are classified as T2DM, which is caused by insufficient insulin secretion, insulin resistance in tissues, and a lack of insulin response (3). Inflammation exacerbates insulin

resistance and hyperglycemia, which are the primary contributors to T2DM and its associated chronic complications (4) .

In 2021, around 536.6 million people aged 20-79 had diabetes, which includes 10.5% of the population (5). By 2045, this is expected to rise to 12.2%, with 783.2 million people being at risk [3]. In Iran, more than 5 million people over the age 25 have diabetes, and 7 to 8 million are pre-diabetic, according to the Ministry of Health and Non-Communicable Diseases. Diabetes increases the risk of coronary heart disease, ischemic stroke, and vascular disease deaths (6). T2DM has a complex polygenic nature, and most of the identified gene loci influence this disease primary through effects on insulin secretion. However, some genomic loci also increase the risk of T2DM by decreasing insulin function (7).

MicroRNA (miRNA) is a type of RNA that does not code for proteins. It is composed of ~22 nucleotides (8). During the process of post-transcription, miRs can regulate the expression of target genes. It is estimated that there are over 1000 miRNA coding genes in the human genome that regulate the expression of at least 30% of protein-coding genes. Additionally, one miRNA alone can exert regulatory effects on multiple mRNAs (9). miRs are associated with several complex diseases, such as T2DM, where they seem to play a role in the development of inflammation (10), fat deposition (11), and pancreatic β-cell apoptosis (12). Additionally, studies have been conducted to shed light on the functional importance of miRs in the proliferation of smooth muscle cells, oxidative stress, and energy metabolism (13), all of which are related to T2DM and its complications (14).

Pancreatic beta cells and insulin target tissues express a set of miRNAs that regulate insulin production, secretion, and action (15). Research has revealed that miRNAs present in the bloodstream can accurately predict the onset and advancement of diabetes (16). In clinical diagnosis, a biomarker is a biological indicator that can predict an important endpoint or intermediate outcome (17). Medical conditions are associated with genetic variants, such as single-nucleotide polymorphisms (SNPs) and chromosomal abnormalities, which are analyzed by genomics (18). Various studies have highlighted the effectiveness of miRNAs as biomarkers (19). MiRNA146a, encoded by miR146a on chromosome 5q33.3, regulates genes in T2DM development and its complications, particularly in TLR signaling pathways of the innate immune system (20). Decreased expression of miR146a can result in a decline in TLR gene expression, cytokine production, and other signaling pathways. Research indicates that miR-146a interacts directly with IRAK1 and TRAF6, ultimately decreasing inflammatory cytokine production in macrophages. Patients with T2DM have been observed to exhibit significantly lower levels of miR-146a (21).

MiR-196a2, encoded by mIR196A2 on chromosome 12q13.13, is an important member of the miRNA-196 precursor family located in the homeobox (HOX) clusters in the human genome (22). It's noteworthy that mature miR-196a triggers the AKT signaling pathway and contributes to the advancement of type 2 diabetes. On the other hand, miR-196 increases the expression of the ANXA1 gene in hyperglycemic patients (23)

The presence of SNPs in miRNA genes may disrupt target mRNA regulation by affecting miRNA synthesis, secretion, and maturation, leading to changes in miRNA function [19]. The association between miR-146a and miR-196a2 polymorphisms and diabetes has been investigated in several studies; however, the results were inconsistent (24-27) Given the inconsistent results reported in prior studies and the biological plausibility of miR-146a and miR-146a2 involvement in T2DM pathogenesis, this study aimed to evaluate the association between three SNPs (rs57095329, rs2910164, and rs11614913) and T2DM in an Iranian population.

2. Methods

SUBJECTS

This case–control study included 100 patients diagnosed with type 2 diabetes mellitus (T2DM) and 100 age- and sex-matched healthy individuals as controls. Participants were recruited from the Gholhak Clinical Laboratory in Tehran, IRAN. Diagnosis of T2DM was based on the American Diabetes Association (ADA) criteria, including one or more of the following: fasting blood sugar ≥ 126 mg/dl, oral glucose tolerance test after 2 hours (OGTT) ≥ 200 mg/dl, random glucose ≥ 200 mg/dl, plasma glucose concentration 2 hours after consuming 75 grams of glucose ≥ 11.1 mM, plasma glucose concentration in fasting state ≥ 126mg/dl (7.0mmol/L), increase in HBA1C level at least 6.5%, or ongoing treatment for diabetes (48 mmol/mol). Control individuals were defined as having FBS < 100 mg/dl, OGTT < 140 mg/dl after 2 hours, HbA1c < 6%, with no personal history of diabetes or malignancies. Exclusion criteria included age below 19 or above 80 years, chemotherapy or radiotherapy exposure, history of cancer, body mass index (BMI) <30, hypertension, stroke, or cardiovascular diseases (24). Written informed consent was obtained from each participant. The study was approved by the Ethics Committee of Islamic Azad University, Tehran-Shargh branch. Peripheral blood samples were collected, and genomic DNA was extracted using the DNsol mini kit™ (ROJE Co., Tehran, Iran) according to the manufacturer's instructions. The extracted DNA was stored at -20 °C

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until analysis.

GENOTYPING

The genotyping of *miR-146a* rs2910164 and *miR-196a2* rs11614913 was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using specific primer sequences and restriction enzymes.

For *miR-146a* rs2910164, the following primers were used:

- Forward: 5′-CTC TGA ACC ATC TCT CTG AAA AGC C-3′
- Reverse: 5′-TTG GTC ACA GGA ACT CAC ACT C-3′

For *miR-196a2* rs11614913:

- Forward: 5′-TCA ACT GAT CTG TGG CTT AGG TAG-3′
- Reverse: 5′-TAC ACC CAC TTT GCC CTA TCT G-3′

PCR was performed with an initial denaturation at 95°C for 5 minutes, followed by 30 cycles (95°C for 40 sec, 60°C for 40 sec, and 72°C for 40 sec), and a final extension at 72°C for 10 minutes. PCR products were digested using 5U of *Taa1* (for *miR-146a* rs2910164) and *MnlI* (for *miR-196a2* rs11614913) at 37°C for 18 hours. The digested PCR products were separated on polyacrylamide gels and visualized via silver staining.

The *miR-146a* rs2910164 PCR product (249bp) yielded three fragments of 129bp, 77bp, and 43bp for the wild-type genotype (GG). The (CC) genotype produced four fragments of 129bp, 45bp, 43bp, and 32bp, while the heterozygous (GC) showed five fragments of 147bp, 77bp, 45bp, 43bp, and 32bp bands.

In case of *miRNA-196a2* rs11614913 polymorphism, the PCR product (183bp) was digested into two fragments of 114bp and 64bp, which were indicative of the TT genotype. An undigested 183bp band represented the CC genotype, and three bands of 183bp, 114bp, and 69bp represented the heterozygous CT genotype.

Genotype analysis of *miR-146a* rs57095329 was carried out by allele-specific amplification refractory mutation system polymerase chain reaction (ARMS-PCR) using the following specific primers:

- A-allele: 5′-CGG GGC TGC GGA GAG TAA AGA-3′,
- G-allele: 5′-CGG GGC TGC GGA GAG TAA AGG-3′,
- common reverse primer: 5′-TTG GAG CAC GTG TCA GGA GCA G-3′ to amplify a 159bp product.

The PCR conditions included an initial denaturation at 95°C for 5 min, followed by 28 cycles (95°C for 50 sec, annealing at 65°C for 50 sec, extension at 72°C for 50 sec), and a final extension at 72°C for 5 minutes. PCR products were electrophoresed on 1.5% agarose gel, and SafeStain was used for band visualization.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared between groups using the independent Student's t-test. Categorical variables, including genotype and allele frequencies, were expressed as numbers and percentages and compared using the Chi-square ($\chi 2$) test.

Hardy-Weinberg equilibrium (HWE) was assessed in the control group to verify the representativeness of the sample population. Associations between genotypes and the risk of T2DM were evaluated using odds ratios (OR) and 95% confidence intervals (CI), calculated via logistic regression models. A two-tailed P-value of less than 0.05 was considered statistically significant. No correction for multiple comparisons was applied unless otherwise specified.

3. Results

CHARACTERISTICS OF THE POPULATION

The clinical and demographic features of the study participants are summarized in Table 1. Significant differences were observed between T2DM patients and healthy controls in fasting blood glucose, BMI, and triglyceride levels (P <0.001). Interestingly, the mean age in the control group was slightly higher than the average age of patients in the T2DM group (P = 0.003). Additionally, the mean of triglycerides and BMI were significantly higher in the patient group than in the control group (P <0.001). However, there were no statistically significant differences in sex distribution or total cholesterol levels between T2DM patients and controls (P> 0.05).

ASSOCIATION OF miR-146a rs2910164 (C>G) with T2DM

The genotype distributions of *miR-146a* rs2910164 polymorphism were in Hardy–Weinberg equilibrium in the control group (P>0.05). The frequency of the G allele was 24% in controls and 36% in the T2DM patients. GC heterozygotes revealed five bands (32bp, 43bp, 45bp, 77bp, and 147bp), while individuals with CC genotype produced four bands (32bp, 43bp, 45bp and 129bp). A significant association was found between the GG genotype and an increased risk of T2DM (OR = 12.11, 95% CI = 1.36-7.9, P=0.003), despite the GG genotype being completely absent in the control group and present in 6% of T2DM patient (table 2).

ASSOCIATION OF miR-196a2 rs11614913 (C>T) with T2DM

No deviation from Hardy–Weinberg equilibrium was observed for *miR-196a2* rs11614913 in either group (P>0.05). The T allele frequency was 42% in T2DM patients compared to 30% in controls. A statistically significant association was found between the TT genotype and an increased T2DM risk (OR = 4.36, 95% CI = 1.13-55.84, P=0.006) (table 2).

ASSOCIATION OF miR146a rs57095329 (A>G) with T2DM

The genotype distribution of *miR-146a* rs57095329 did not show significant deviation from Hardy–Weinberg equilibrium (P>0.05). The frequency of the G allele was 51% in the controls and 27% in the T2DM group, respectively. A strong association was observed between the GG genotype and increased susceptibility to T2DM (OR = 8.37, 95% CI = 3.07 - 22.82, P<0.0001) (table 2).

Table1. Demographic and clinical characteristics of the cases and control

Characteristic		Groups		P-value
		Control(N=100)	Diabetes(N=100)	
Gender	Female	50	50	
	Male	50	50	
Mean Ages (years)		57.60 ± 7.4	53.72 ± 9.241	0.003
Diabetes duration (years)			6.50 ± 3.86	
Mean B.M.I (kg/m2)		27.46 ± 4.27	29.85 ± 5.05	0.000
FPG (mg/dl)		93.40 ± 6.365	173.04 ± 82.157	0.000
HbA1c (%)			8.5 ± 2.64	
TG (mg/dl)		133.07 ± 57.34	154.63 ± 56.06	0.000
TC (mg/dl)		187.6 ± 53.42	181.061 ± 56.05	0.059

BMI: body mass index, FPG: fasting plasma glucose, HbA1c: hemoglobinA1c, TG: triglyceride, TC: total cholesterol

Table2. Frequency distributions of *miR-146a* (rs2910164 and rs57095329C) genotypes and *miR-196a2* rs11614913 polymorphism rate among the T2DM and control group.

Genotype	Controls n=100(%)	T2DM n=100(%)	OR (95% CI)	p value
miR-146a rs2910164C>G				
CC	52(52%)	34(34%)	1	
GC	48(48%)	60(60%)	1.68(1.57-9.63)	
GG	**0**	**6 (6%)**	**12.11(1.36-7.9)**	**0.03**
C	76(76%)	64(64%)		
G	24(24%)	36(36%)		
miR-196a2 rs11614913C>T				
CC	45(45%)	33(33%)	1	
CT	50(50%)	50(50%)	1.36(0.75-2.47)	
TT	**5(5%)**	**17(17%)**	**4.36(1.13-55.84)**	**0.006**
C	70(70%)	58(58%)		
T	30(30%)	42(42%)		
miR-146a rs57095329A>G				
AA	53(53%)	19(19%)	1	
AG	40(40%)	60(60%)	2.00(0.78-5.14)	
GG	**7(7%)**	**21(21%)**	**8.37(3.07-22.82)**	**<0.0001**
A	49(49%)	73(73%)		
G	51(51%)	27(27%)		

Variables	*miR-146a* rs2910164(GC)		*miR-196a2* rs11614913(TC+CC)		*miR-146a* rs57095329(AG+GG)	
	AOR (95% CI)	P-value	AOR (95% CI)	AOR (95% CI)	P-value	AOR (95% CI)
Body mass index, kg/m^2						
<28	0.594 (0.370-0.955)	0.31	0.624 (0.388-1.003)	0.052	0.779 (0.492-1.235)	0.289
≥28	0.826 (0.506-1.348)	0.444	0.899 (0.558-1.446)	0.66	0.697 (0.428-1.135)	0.147
Glycosylated hemoglobin, type A1C eAg, mg/dl						
≤125.5	0.717 (0.453-1.135)	0.155	0.702 (0.447-1.103)	0.125	0.787 (0.477-1.297)	0.347
>125.5	0.566 (0.341-0.940)	0.058	0.623 (0.370-1.049)	0.075	0.844 (0.504-1.412)	0.518
Total cholesterol, mg/dl						
≤240	0.910 (0.461-1.797)	0.787	0.652 (0.343-1.238)	0.191	0.660 (0.425-1.027)	0.065
>240	0.875 (0.510-1.501)	0.627	0.693 (0.448-1.072)	0.1	0.703 (0.405-1.219)	0.209
Triglyceride, mg/dl						
<216	0.573 (0.375-0.876)	0. 15	1.825 (0.566-5.886)	0.314	0.229 (0.093-0.561)	0.086
≥216	0.393 (0.071-2.184)	0.286	1.792 (0.513-6.264)	0.361	1.319 (0.559-3.115)	0.528
Low-density lipoprotein-cholesterol, mg/dl						
≤130	0.831 (0.551-1.252)	0.375	0.852 (0.511-1.420)	0.539	0.565 (0.356-0.896)	0.075
>130	2.114 (0.413-10.817)	0.369	0.712 (0.433-1.171)	0.181	0.750 (0.475-1.183)	0.215

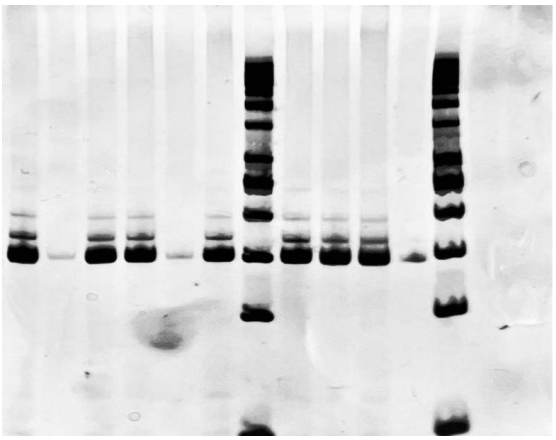

Figure1. L1,2 and 10,11: AA Homozygous, L3,4 and L8,9: AG Heterozygote,
L5,6: GG homozygous, L7 and 12: 50bp DNA ladder, L12: NTC.

4. Discussion

Obesity and type 2 diabetes mellitus (T2DM) are associated with immune system dysregulation, affecting multiple tissues and leading to altered levels of cytokines and chemokines, increased leukocyte infiltration, apoptosis, and tissue fibrosis. Consequently, chronic inflammation plays a central role in the development of T2DM (28). In parallel, microRNAs (miRNAs) particularly miR-146a and miR-196a2, have emerged as key regulators of immune and inflammatory responses, lipid deposition, and pancreatic β-cell apoptosis in complex diseases such as T2DM (14). In this case-control study, we investigated the association of three SNPs- rs57095329, rs2910164 in miR-146a, and rs11614913 in miR-196a2 gene- with T2DM susceptibility in an Iranian population.

miR-146a rs2910164 (C>G)

Our findings indicated that the GG genotype of rs2910164 increased the likelihood of T2DM by 12.11-fold. This polymorphism involves a G-to-C substitution in the precursor stem region of miR-146a, changing a GU to CU pair, thereby altering miRNA secondary structure and its interaction with mRNA targets such as IRAK2, FADD, DTAT1, and NFKB, all of which are involved in inflammatory pathways.

Previous studies have shown mixed results. Alipoor et al. (2016) found a higher frequency of the CC genotype in Iranian diabetic patients, associated with elevated blood glucose, cholesterol, and HbAlc levels, possibly due to structural instability caused by the substitution of G to C in the miR-146a sequence (21). Furthermore, miR-146a levels were found to be significantly lower in peripheral blood mononuclear cells (PBMCs) and plasma of T2DM patients compared to healthy controls. Notably, individuals with the GG genotype exhibited higher miR-146a expression in plasma samples and PBMCs compared to CC genotype carriers (6).

Similarly, Shankaran et al. (2019) reported that the C allele and CC genotype were associated with T2DM susceptibility in the Indian populations (29). A meta-analysis also supported the association between rs2910164 and T2DM susceptibility (30). However, other studies have reported conflicting findings, with some indicating the G allele as protective (24, 25, 31), while Wang et al. found no association between the G allele and T2DM risk (27). Huang et al. (2021) also reported a reduced T2DM risk in carriers of the G allele (14). These inconsistencies may arise from differences in ethnicity, sample sizes, or study designs emphasizing the need for additional well-matched investigations in the future.

miR-146a rs57095329 (A>G)

The rs57095329 polymorphism resides in the promoter region of miR-146a, overlapping the binding site of ETS1 transcription factor. The A allele of this polymorphism has been shown to impair ETS1 binding, leading to increased expression of miR-146a. In a study by Yong et al. (2013), circulating miR-146a levels were particularly elevated in patients with T2DM. Interestingly, individuals with lower circulating levels of miR146a had lower risk of T2DM, suggesting a complex expression-disease relationship (32).

Our study demonstrated that individuals with the GG genotype at rs57095329 had a significantly increased risk of T2DM by 8.37 times. This is supported by Luo et al. (2011), who reported lower levels of mature miR-146a expression in individuals with the GG genotype compared to those with AA or AG, suggesting that this variant may regulate transcriptional activity and miRNA expression (33). However, these findings contrast with other Iranian studies suggesting that GG genotype is protective. These discrepancies may be due to ethnic variation and differences in recruitment criteria.

miR-196a2 rs11614913 (C>T)

The rs11614913 polymorphism, is located on the 3p arm of mature miR-196a2 (34). Several investigations found that the C allele of rs11614913 enhances miRNA maturation and expression (35, 36). In the present study, we observed that the TT genotype was associated with significantly increased susceptibility to T2DM. Ghanbari et al reported that the C allele was associated with a reduced waist-to-hip ratio and weight loss (37). Conversely, Ibrahimi et al found an association between the T allele and CT genotype and an increased T2DM risk in a Saudi Arabian population (26). Huang et al (2021) reported that the C allele reduced the risk of developing T2DM among smokers [14]. This suggests that environmental factors may influence the impact of the C allele.

Moreover, Yin et al. also indicated that the gene-environment interactions involving rs11614913 were also linked to lung cancer risk (38). This implies that the relationship between the rs11614913 locus and the occurrence of T2DM may be influenced by environmental risk factors. Since individual miRNA loci, such as miR-196a2 rs11614913, exert only modest effects on T2DM susceptibility, their impact may be masked or diluted by gene-environment interactions (14).

5. Conclusion

In conclusion, this population-based case–control study demonstrates that rs2910164 and rs57095329 polymorphisms in miR-146a, and rs11614913 in miR-196a2, are significantly associated with T2DM risk in an Iranian population. These findings highlight the role of miRNA-related genetic variants in T2DM susceptibility and underscore the need for larger, multi-ethnic studies incorporating gene–environment interactions and **functional analyses.

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Ethical Considerations and Compliance with Ethical Guidelines

This study was approved by the Ethics Committee of the University of East Tehran Branch (Ghiamdasht) (Code: IR.IAU.ET.REC.1401.042).

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Conflict of interest

The authors declare no conflict of interest.

AI Using Declaration

The authors declare no artificial intelligent chatbot use.

Author's contributions

All authors equally contributed to preparing this article.

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