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ORIGINAL ARTICLE

rs4759314 HOTAIR Polymorphism in Type Two Diabetic Patients

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ABSTRACT

Background: Deficiencies in islet β-cell activity, which can arise from genetic, environmental, or immunological factors, result in a flat-out or relative decrease in insulin emission, which is the hallmark of T2DM. Gene polymorphisms and the incidence of type 2 diabetes have been linked in numerous studies. There is a correlation between T2DM risk and single-nucleotide polymorphisms (SNPs) found in the intergenic zones of multiple potential genes. lncRNAs are in excess of 200 nucleotides long. lncRNAs have been linked to type 2 diabetes in many ethnic groups.

HOX antisense RNA transcription (HOTAIR) is a well-characterized long noncoding RNA that is found on human chromosome 12q13. Finding out if the rs4759314 HOTAIR gene polymorphism is linked to T2DM is the goal of the current study

Methods: This study was carried out on 192 subjects (96 healthy controls, and 96 non-insulin-dependent diabetic patients. HOTAIR genotype was determined by T-ARMS-PCR

Results: The predominance of the polymorphic genotype of HOTAIR polymorphism (GG) was essentially expanded in type two diabetic patients contrasted with the healthy group (15.6% vs. 5.2%). ($P<0.01$). Compared to carriers of the AA genotype, those carrying the GG genotype had the probability of getting T2DM four times higher (OR=3.92).

Conclusions: The Egyptian people may be more susceptible to T2DM if they have the GG genotype of the HOTAIR rs4759314 polymorphism.

Keywords: HOTAIR polymorphism; long non-coding RNA; type 2 diabetes mellitus.

INTRODUCTION

Anomalous protein and lipid metabolism, as well as hyperglycemia, are hallmarks of type 2 diabetes (T2DM), a complicated metabolic illness. Standing as the sixth most frequent reason for demise worldwide, T2DM is regarded as a major health concern [1].

Diabetes mellitus affects 463 million individuals globally (ages 18 to 99), By 2045, it's expected to reach 700 million, according to a 2019 International Diabetes Federation (IDF) poll. [2]. Approximately 15.6% of all adults in Egypt between the ages of 20 and 79 have T2DM [3]. genetic variations and the incidence of T2D have been linked in numerous studies [2]. T2DM risk has been linked to single-nucleotide polymorphisms (SNPs) in intergenic zones of several potential genes. [4]. Less than 2% of the human genome is composed of coding successions, while over 90% of the genome is composed of noncoding successions [5]. Noncoding successions are incapable of synthesizing proteins, but they are connected to a wide range of biochemical procedures, like coordinating the

creation of proteins and maintaining transcriptional gene expression [6] [7].

lncRNAs are in excess of 200 nucleotides long and are required for a variety of biological functions, including transcription regulation, translation, and epigenetic modification [8]. Different ethnic groups have been shown to have lncRNAs linked to type 2 diabetes. [9] Research has indicated that lncRNAs play an integral role in preserving the balance of glucose, which subsequently in fact plays an aspect in the genesis of diabetes and its sequelae [10].

An extensively researched long noncoding RNA called HOTAIR is found on human chromosome 12q13 [11]. It has been demonstrated that HOTAIR offers a substantial part in controlling malignant cell expansion and migration. [12]. Furthermore, HOTAIR expands atherosclerosis and creates oxidative stress by affecting miR-330 in phagocytes, a microRNA that contributes to impaired insulin modulation. [13]. This study set out to determine the correlation between the Egyptian population's vulnerability to T2DM and the polymorphism of the HOTAIR (rs4759314).

METHODS

In the Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Zagazig University, a case-control study was conducted. The Zagazig University Institutional Research Board accepted the study's protocol (IRB#: 10521-7-3-2023). All patients and healthy individuals provided written informed permission. There were 192 participants in this study, divided into two groups. 96 healthy individuals without a background of any chronic condition, as well as no family history of any disease that would have interfered with my study, formed the control group. The diseased group included (96) non-insulin-dependent diabetic patients.

The American Diabetes Association (ADA) criteria were used to diagnose all patients: blood glucose >126 mg/dl during the fasting period, blood glucose >200 mg/dl during the 2-hour postprandial period, and HbA1c > 6.5% in individuals exhibiting the characteristic hyperglycemia symptoms, as well as random blood glucose > 200 mg/dl.

The following was applied to both the patients and the controls: complete history evaluation of the length of diabetes, the history of prior medications, and any family background of type 2 diabetes mellitus. It also includes a full clinical assessment with measurement of fasting blood glucose.

Specimen collection

Three milliliters of fasting venous blood samples were taken from median cubital veins in an entirely aseptic manner following skin sterilization with ethyl alcohol swabs. To estimate the fasting blood glucose level, one milliliter of sodium fluoride was collected. In order to extract genomic DNA, two milliliters were collected and kept at -20°C in sterile EDTA tubes.

Biochemical assay

Using the enzymatic colorimetric technique and SPINREACT (Girona, Spain), the fasting blood glucose level was measured. **[14]**.

DNA extraction and PCR (T-ARMS PCR) analysis

Utilizing the Blood Genomic DNA isolation pack (Solarbio-China-Cat#D1800), genomic DNA could be extracted from blood leukocytes. rs4759314 HOTAIR was found using T-ARMS-PCR, which employed two outside and two inside primers as shown in Table 1

A final volume of 20 µl was used for the PCR, which included 10 µl of 2x i-Taq™ PCR Master Mix (Geneaid Biotech Ltd), 1 ul of each primer (Biolegio, Nijmegen, Netherland), 5µl of genomic DNA and 3 ul of deionized water.

DNA thermal cycler Eppendorf AG 22331 (Master cycler-Flexid), Serial No. 6331DG106332, was used to carry out the amplification. Based on the subsequent procedure: The initial denaturation was conducted at 94°C for four minutes, followed by thirty-five runs of denaturation at 94°C for 45 seconds, annealing at 54.5°C for 45 seconds, elongation at 72°C for 55 seconds, and last extension at 72°C for ten minutes. PCR findings had been separated on a 2% agarose gel and colored with ethidium bromide. and were visible under a UV transilluminator. The product sizes were as follows: 121 bp for the G allele, 181 bp for the A allele, and 24 bp for the external control band.

Statistical Analysis

The entire statistical evaluations were conducted by applying the latest version of SPSS (Chicago, IL, USA). Chi-squared and two-sided unpaired t-tests were employed for comparing data between cases and controls, whereas Fisher's exact (F) assessment was implemented in cases with small sample numbers. P-values less than 0.05 are deemed relevant.

RESULTS

192 subjects were involved in this study, comprising 96 individuals with diabetes and 96 healthy controls. With the exception of BMI, which was higher on average in patients with DM ($P<0.001$), the majority

of variable distributions, such as age, sex, and length of disease, were similar between the diabetic group and normal group (p-value > 0.05) as shown in Table 2.

Also, Table 3 illustrates the distribution of clinical and biological parameters in diabetic cases and controls. Diabetic individuals had greatly higher mean fasting blood sugar (p<.001), triglyceride (p<.001), total cholesterol (p<.001), low-density lipoprotein (p<.001), and HbA1c (p<.001) compared to healthy people. Compared to diabetic individuals, healthy people had considerably greater HDL (p<.001).

The genotype distribution of the targeted SNPs and their associations with T2DM risk are shown in Table 4. In both the cases and the controls, the genotype frequencies of SNPs matched the Hardy-Weinberg equilibrium (HWE) (p-value > 0.05). The results showed that the two groups genotype and allele frequency of the HOTAIR gene polymorphism differed statistically substantially As the type 2 diabetic patients had a greater (G) allele than the control group (39.1% vs. 28.1%). Compared to carriers of the A allele, carriers of the G allele had a higher chance of developing T2DM twice (OR = 1.64). This table demonstrated that, in type 2 diabetic patients, the frequency of the HOTAIR gene's GG genotype was substantially greater than in control subjects (15.6% vs. 5.2%). Compared to those with the AA genotype, carriers of the GG genotype had a four times greater chance of developing T2DM (OR = 3.92). The AA genotype was found in the control group (49%) and T2DM group (37.5%). The distribution of AA genotypes did not show any discernible differences. The AG genotype was shown in the (45.8%) control group and the (46.9%) T2DM group. There were no obvious disparities in the AG genotype dispersion. suggesting that a significant correlation may exist between the G allele carrier and A higher probability of diabetes of the second kind.

In relation to the demographic information of Individuals having the second type of Diabetes who were classified based on HOTAIR gene polymorphism, we discovered Remarkably substantial variations between the various HOTAIR genotypes and BMI as well as the duration of the disease; Individuals carrying the GG genotype had more pronounced BMI. (P=0.007), while those with the AA genotype had a longer disease duration (P=0.02) as shown in Table 5.

Upon comparing type 2 diabetic patients' laboratory data with their HOTAIR genotypes (GG, AG, and AA), we discovered significant correlations between the various HOTAIR genotypes and levels of cholesterol, LDL, and triglycerides. Notably, People carrying the GG genotype observed increased levels of cholesterol, LDL, and triglycerides (P<0.05). Higher levels of triglycerides, LDL, and cholesterol were more common in GG individuals as shown in Table 6.

Table 1: Primers of HOTAIR

forward outer primer	5′-AAACCATATCCTGACAGAAGCCAAATAC-3′
reverse outer primer	5′- CCAAGGTAGGGAAGTCTCTATTTCTCTG-3′
Forward inner primer (G allele):	5′-GCATGGAAGAGATATAAACAGGCGAA-3′
reverse inner primer (A allele):	5′- TTATCACGTTTTATTAACTTGCATCCTCC-3′

Table 2: Demographic data among studied groups

Variables		**Control (n=96)**	**T2DM (n=96)**	**P Value**
Age (years)	Mean ± SD	51.9 ± 6.71	54.1 ± 8.62	0.06[1]
	Range	(38 – 62)	(35 – 75)	
Sex (n. %)	Male	51 (53.1%)	45 (46.9%)	0.39[2]
	Female	45 (46.9%)	51 (53.1%)	
BMI (kg/m^2)	Mean ± SD	26.6 ± 1.9	32.1 ± 5.11	**<0.001[3] ***
	Range	(23.4 – 29.8)	(21.6 – 41.1)	
Duration of DM *(years)*	Mean ± SD	-	9.83 ± 3.5	-
	Range	-	(3 – 18)	

SD; standard deviation, BMI;basal metabolic index ,kg: kilogram; m2:square meter,T2DM; type 2 diabetes, Non-significant: P >0.05, Significant: P ≤0.05

Table 3: Laboratory data among studied groups

Variables		Control (n=32)	T2DM (n=32)	P Value
Fasting blood glucose (mg/dl)	Median (IQR)	102 (6.5)	167.5 (56.25)	**<0.001[2] ***
	Range	(85 – 109)	(129 – 285)	
HbA1C (%)	Median (IQR)	4.9 (0.5)	7.9 (1.3)	**<0.001[2] ***
	Range	(4.3 – 5.6)	(6.5 – 11.4)	
Total cholesterol (mg/dl)	Mean ± SD	131.1 ± 10.45	172.3 ± 24.4	**<0.001[1] ***
	Range	(110 – 152)	(133 – 220)	
HDL-C (mg/dl)	Mean ± SD	62.9 ± 7.39	51.1 ± 8.88	**<0.001[1] ***
	Range	(50 – 75)	(31 – 66)	
LDL-C (mg/dl)	Median (IQR)	42.8 (22)	87.8 (43.1)	**<0.001[2] ***
	Range	(14 – 74.4)	(41.4 – 154)	
Triglycerides (mg/dl)	Median (IQR)	117.5 (23.25)	164.5 (23.25)	**<0.001[2] ***
	Range	(94 – 139)	(130 – 181)	

T2DM: type 2 diabetes, HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol, mg: milligram; dL: deciliter, Significant: P ≤0.05

Table 4: Genotype of HOTAIR gene polymorphism among studied patients

Variables		Control no (%)	T2D no (%)	OR (95% CI)	P Value
Genotype	AA	47 (49%)	36 (37.5%)		
	AG	44 (45.8%)	45 (46.9%)	1.34 (0.73 – 2.44)	0.35
	GG	5 (5.2%)	15 (15.6%)	3.92 (1.3 – 11.78)	**0.01***
Allele	A	138 (71.9%)	117 (60.9%)		
	G	54 (28.1%)	75 (39.1%)	1.64 (1.04 – 2.57)	**0.02***

T2D; type2 diabetes, OR; odds ratio, Significant: P ≤0.05

Table (5): Relation between genotype of HOTAIR gene polymorphism and demographic data among type 2 diabetic patients

Variables		Genotype AA (n=36)	Genotype AG (n=45)	Genotype GG (n=15)	P Value
Age (years)	Mean ± SD	55.3 ± 10.52	54 ± 6.75	51.4 ± 8.44	
	Range	(35 – 75)	(41 – 69)	(45 – 67)	0.35[1]
Sex (n. %)	Male	15 (41.7%)	21 (46.7%)	9 (60%)	
	Female	21 (58.3%)	24 (53.3%)	6 (40%)	0.49[2]
BMI (kg/m^2)	Median (IQR)	30 (4.88)	31.4 (8.1)	34.2 (9.4)	
	Range	(21.6 – 39.9)	(26.5 – 41.1)	(27.7 – 40.9)	**0.007[2] ***
Duration *(years)*	Median (IQR)	10.5 (3.25)	9 (7)	8.5 (3)	
	Range	(7 – 16)	(3 – 18)	(5 – 12)	0.02[2]

SD; standard deviation, BMI;basal metabolic index, kg: kilogram; m2:square meter; Significant: P ≤0.05

Table 6: Relation between genotype of HOTAIR gene polymorphism and laboratory data among type 2 diabetic patients

Variables		Genotype AA (n=36)	Genotype AG (n=45)	Genotype GG (n=15)	P Value
Fasting blood glucose *(mg/dl)*	Median (IQR)	194.5 (56.75)	165 (56)	147 (69)	0.17
	Range	(131 – 254)	(134 – 285)	(129 – 246)	
HbA1C *(%)*	Median (IQR)	8.1 (1.02)	7.8 (1.5)	8.5 (1.8)	0.09
	Range	(6.5 – 10.1)	(6.5 – 9.5)	(7.1 – 11.4)	
Cholesterol *(mg/dl)*	Median (IQR)	172.5 (31.75)	160 (55)	197 (20)	**0.003***
	Range	(148 – 206)	(133 – 198)	(140 – 220)	
HDL-C (mg/dl)	Median (IQR)	50 (15.3)	58 (12)	57 (17)	0.08
	Range	(36 – 68)	(39 – 66)	(31 – 62)	
LDL-C (mg/dl)	Median (IQR)	93.3 (29.55)	73.4 (59.8)	111.8 (8.8)	**0.007 ***
	Range	(51.4 – 128)	(41.4 ± 121)	(52 – 154)	
Triglycerides *(mg/dl)*	Median (IQR)	164.5 (18)	153 (26)	175 (23)	**0.03 ***
	Range	(149 – 181)	(130 – 179)	(145 – 177)	

HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; mg: milligram; dL: deciliter, Significant: P ≤0.05

DISCUSSION

The long-term metabolic condition known as diabetes mellitus (DM) is explained as raised blood sugar levels., interrupts the breakdown of lipids and proteins., and a partial or absolute lack of insulin production due to a combination of environmental and genetic variables [15]. The most prevalent type of diabetes, T2DM, constitutes above ninety percent of all cases. [16]. lncRNAs, which have a length of more than 200 nucleotides, are essential for a variety of biological functions, including transcription regulation, translation, and epigenetic modification [8].

HOTAIR is a well-studied long noncoding RNA that exists on human chromosome 12q13 [2].

The purpose of our research was to determine whether the HOTAIR gene polymorphism and T2DM susceptibility are related. We identified subjects with HOTAIR polymorphism in our populations using the ARMS-PCR technique.

Two groups were included in our study, one with 96 participants as the control group and another with 96 patients with T2DM. Age, gender, and illness duration were matched between the two groups, and there was no statistically significant difference. However, the BMI of T2DM was substantially greater than that of the other group.

Sargazi, Ravanbakhsh, Nia, Mirinejad, Sheervalilou, Majidpour, Danesh and Saravani [17] conducted research that supports our findings by revealing no substantial variations in age or sex distribution between the two groups under study. Furthermore, there was an important distinction ($p < 0.001$) in BMI between T2DM patients and the controls.

In reference to laboratory data, our findings demonstrated a substantial variance in readings for fasting blood glucose, HbA1C, and overall cholesterol., LDL-C, triglycerides, and HDL-C between the two groups. For the most part, all laboratory data were A greater number of individuals having diabetes of the second kind., except HDL-C, which was greater in the unaffected group. ($P<0.001$).

Our research confirms some findings and contradicts others from Sargazi and Ravanbakhsh's study [17], which found that while There was no substantial change. in HDL-c and TC among the participants, there was considerable variation in FBG, LDL-c, HbA1C, and TG levels among type 2 diabetic patients and their counterparts.

Our research confirms some findings and contradicts others of Sargazi, Ravanbakhsh, Nia, Mirinejad, Sheervalilou, Majidpour, Danesh and Saravani [17] who found that while there was no significant difference in HDL-c and TC among the participants, there was a significant difference in FBG, LDL-c, HbA1C, and TG in type 2 diabetic patients compared to the control group.

It has been laid out that HOTAIR is engaged with hepatic insulin intolerance. by decreasing the Akt/glycogen synthase kinase-3β (GSK-3β) pathway and restricting sirtuin 1, a possible therapy to alleviate insulin intolerance and diabetes. Furthermore, it was discovered that upon stimulation of the TNFA, HOTAIR expression was significantly elevated. In children and adolescents [18]. TNFA has a role in the pathophysiology of the first kind of diabetes and a variety of other inflammatory illnesses [19].

The prevalence of the HOTAIR GG genotype was substantially greater in the people with type 2 diabetes group than in the unaffected group., according to our data, suggesting that the rs4759314 GG genetic variation may be a contributory factor for the second kind of diabetes. Genetic heterogeneity may have led to different findings in different groups. This is consistent with the findings of Sargazi, Ravanbakhsh, Nia, Mirinejad, Sheervalilou, Majidpour, Danesh and Saravani [17] who demonstrated that the HOTAIR gene (rs4759314) variant had a role in T2DM in the Iranian population Sargazi, Ravanbakhsh, Nia, Mirinejad, Sheervalilou, Majidpour, Danesh and Saravani [17] came to the same conclusion, demonstrating that the patients with diabetes had a significantly higher GG genotype than the unaffected group (P<0.001) and that the patients with diabetes had a higher frequency of the (G) allele (P<0.002). He also discovered that the G allele of (rs4759314) increased danger associated with T2DM. by 1.21 fold.

In a related study, Sathishkumar, Prabu, Mohan and Balasubramanyam [20] found that individuals with type 2 diabetes had higher peripheral blood mononuclear cells expressing HOTAIR, As opposed to controls. Furthermore, a different study revealed that T2DM patients' liver tissues overexpress HOTAIR. [2].

In another study, Ma, Fan, Feng, Chen, Xu, Li, Lin, He, Shi and Liu [21] indicated that HOTAIR focuses on miR-143 and influences its activity. In a group of Iranians, it was previously discovered that miR-143 is linked to the vulnerability of the second kind of diabetes [22].

In a comparable manner, Jiang, Xue, Xu, Song and Zhu [23] suggested that the downregulation of HOTAIR is linked to a reduction in the production of insulin-like growth factor-1 (IGF-1), which impacts glucose breakdown in the body.

By focusing on several genes, these studies have offered an explanation for HOTAIR's role in insulin resistance and glucose metabolism. Consequently, HOTAIR gene polymorphisms may serve as a predictor for different forms of diabetes or associated problems.

According to our research, individuals with the GG genotype had a higher BMI (P=0.007), while those with the AA genotype had a longer disease duration (P=0.02). Furthermore, we discovered that individuals with the GG genotype had greater ranges of cholesterol, LDL, and triglycerides (P<0.05), which means patients with the (G) allele are more likely to increase cholesterol, LDL, and triglycerides levels.

Our research confirms some of the findings of the research; Sargazi, Ravanbakhsh, Nia, Mirinejad, Sheervalilou, Majidpour, Danesh and Saravani [17] who found significant associations between (rs4759314) and fasting blood glucose and LDL-C in T2DM, and significant associations between (rs4759314) and triglycerides in controls.

Conclusions

We concluded that the current study offers proof that HOTAIR rs4759314 contributes to T2DM susceptibility in the Egyptian population, suggesting that HOTAIR (rs4759314) GG may raise the chance of T2DM in Egyptian patients.

Further research on two distinct SNPs (rs920778 and rs1899663) in the HOTAIR-expressing gene is necessary to determine their functions and susceptibility to type 2 diabetes.

Further techniques are required to validate the findings of this investigation. For our investigation, the sample size was somewhat small. Larger samples, other geographies, and ethnic groups must corroborate the findings of our research, as the populations we chose were exclusively Egyptian.

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