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Investigation of Slc30a8 (Rs13266634) Gene Polymorphisms in Type 2 Diabetes Mellitus Patients

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Abstract

Type 2 Diabetes Mellitus (T2DM), a complex metabolic condition, is caused by a number of environmental and genetic factors, as well as their interactions. Many genes associated with T2DM have been discovered through genome-wide association studies. One of these genes is the SLC30A8 gene. T2DM and the SLC30A8 gene are linked to zinc, which is required for insulin secretion and storage. The aim of the research was to look into the relationship between T2DM disease and the rs13266634 polymorphism in the SLC30A8 gene. The research included 80 healthy people and 80 people with type 2 diabetes who were chosen at random from Şanlıurfa. A commercial kit was used to isolate DNA. Following isolation, the SLC30A8 gene region was amplified using PCR and cut with the HpaII enzyme. TT, CT, and CC alleles were discovered after cutting. We used data from 45 diagnosed T2DM cases and 52 confirmed healthy control subjects to detect alleles, and the gel imaging results were reliable and confident. The data analysis was evaluated using the SPSS method. The findings revealed a statistically significant relationship between the patient and control groups and the rs13266634 polymorphism in the SLC30A8 gene. Clarifying the genetic relationship between the rs13266634 polymorphism in the SLC30A8 gene and T2DM disease may aid in identifying genetic predispositions and developing risk profiles.

Keywords: Diabetes mellitus, Type 2 diabetes, polymorphism, SLC30A8 (rs13266634)

Introduction

Diabetes mellitus (DM) is characterized by chronic hyperglycemia and impaired carbohydrate, lipid, and protein metabolism, which is caused by a total or partial inadequacy of insulin secretion or action (1). Type 2 Diabetes Mellitus (T2DM), which has a more complicated etiology, is caused by a combination of genetic and environmental factors (2). This condition is caused by changes in insulin secretion and an increase in insulin resistance (3). Although it is estimated that 382 million adults worldwide had T2DM in 2013 (4), when data from research conducted in 130 countries is considered, this figure corresponds to the value projected by the World Health Organization (WHO) for 2030 in its 2004 proclamation (5). The rising prevalence of diabetes, as well as the associated morbidity, mortality, and financial consequences, is a

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major public health issue on a global scale (6).

Through candidate gene approach studies, nearly 70 genes associated with T2DM have been identified in recent years. One of these genes, the 8 (SLC30A8) gene of the soluble carrier family 30 member, has been linked to an increased risk of type 2 diabetes (7). The SLC30A8 gene encodes the zinc carrier protein component-8, which has eight exons and 369 amino acids and regulates -cell zinc homeostasis (8-11). It is required for zinc transfer from the cytoplasm to intracellular insulin-containing vesicles, which is required for insulin maturation, storage, and secretion. The SLC30A8 zinc transporter gene is found in the insulin-secreting granule. The rs13266634 C to T single nucleotide polymorphism in the SLC30A8 gene causes a nonsynonymous mutation at position 325, changing arginine (R) to tryptophan (W) (12). The SLC30A8 gene causes beta cells to malfunction and moves zinc from the cytoplasm to the vesicles that secrete insulin. Zinc is expressed as a result of binding to pancreatic cells. Insulin release is inhibited by the SLC30A8 gene. T2DM is the result of this (11,13). The SLC30A8 gene has also been shown in vitro and in mouse studies to reduce insulin production and cause insulin crystallization (14,15).

The purpose of the study;

i) To better understand the genetic link between the SLC30A8 gene's rs13266634 polymorphism and T2DM disease,

ii) To ensure that genetic predisposition is detected,

iii) To develop risk profiles,

iv) Its goal is to delay the onset of the disease through diagnosis, treatment, and even early intervention.

Materials and Methods

This study was approved by the Harran University Clinical Research Ethics Committee with the ethics committee decision numbered 21.20.11. In our study, 80 T2DM patients and 80 healthy controls were randomly selected from individuals over the age of 18 who applied to Şanlıurfa Harran University Hospital Internal Medicine Outpatient Clinic. Data from 45 diagnosed T2DM cases and 52 confirmed healthy subjects, which gave reliable results in experimental studies, were included in the study. The World Health Organization (WHO) values established in Turkish nationals (126 mg/dl or >7.0 mmol/L) serve as the basis for the inclusion criteria for T2DM patients. Individuals with normal glucose tolerance (FBG>7.0), over the age of 18, and no history of diabetes in the immediate family were eligible to participate as control participants. The study's participants were aged in years and were classified as either male or female.

In our study, blood was collected from both the T2DM patient and control groups and placed in 3 ml EDTA tubes for genotype analysis. Routine biochemical tests were also performed on the blood samples, and the biochemical parameters' values were obtained.

DNA Isolation: The GeneJET Genomic DNA Purification Kit was used to isolate total DNA in this study (Thermo Scientific, USA). During isolation, the kit's protocol steps were followed. To monitor and control the DNA obtained through isolation, DNA samples were collected and stained with 3 l of 2X DNA loading dye. The samples were loaded onto a 1% agarose gel (Sigma Aldrich, Germany) containing 2.5 µl of SYBR Green dye (Applied Biological Materials, Canada), which made the DNA visible under UV light, and then run at 100 V for 30 minutes. The gel imaging system was used to monitor the isolated DNA (Smart View Pro 1100 Imager System, Major Science).

Amplification of the Target DNA Region by PCR: Alharbi et al. (2021) published primer sequences for amplification of the SLC30A08 gene region (F: 5'-GAA GTT GGA GTC AGA GCA GTC-3'; R: 3'-TGG CCT GTC AAA TTT GGG AA-5'). The PCR was carried out in a Thermal Cycler (BIO-RAD T100TM).

Following 3 minutes of initial denaturation at 95°C, 30 seconds of denaturation at 95°C, 30 seconds of bonding

at 50.5°C, and 45 seconds of elongation at 72°C were performed for a total of 35 cycles. Finally, the reaction was stopped after 5 minutes of holding the samples at 72°C. The PCR mixture used in the replication of the target region is; 15.9 µl dH2O, 2.5 µl 1X Taq DNA polymerase buffer (Thermo Scientific, USA), 2 µl MgCl2 (2.5 M), 0.5 µl 10mM dNTP, 1 µl primer (F), 1 µl primer (R), 0.1 µl Taq DNA polymerase (Thermo Scientific, USA) and 2 µl (90 ng) of template DNA, a total of 25 µl.

Treatment of PCR products with the Restriction Enzyme HpaII: For 5 µL of PCR product in the treatment of PCR products with HpaII restriction enzyme; 9 µL of distilled water, 1 µL of 10X Buffer Tango (Thermo Scientific, USA) and 0.5 µL of HpaII (10 U/µl) (Thermo Scientific, USA) enzyme were mixed. The prepared mixture was incubated at 37°C for 3 hours. Inactivation of the HpaII enzyme was carried out at 65°C for 20 minutes. Cut products were loaded onto a 1.5% agarose gel (Sigma Aldrich, Germany) containing which enables the bands of products to be visualized in UV light 3.5 µl of SYBR Green (Applied Biological Materials, Canada) by adding 5 µl of 2X DNA loading dye. 5 µl of GeneRuler 100 base pair Opti-DNA ladder (Applied Biological Materials, Canada) was used as ladder. The gel was run at 90 V for 30 minutes. After running, the bands were visualized by using the gel imaging system (Smart View Pro 1100 Imager System, Major Science) (Figure 1).

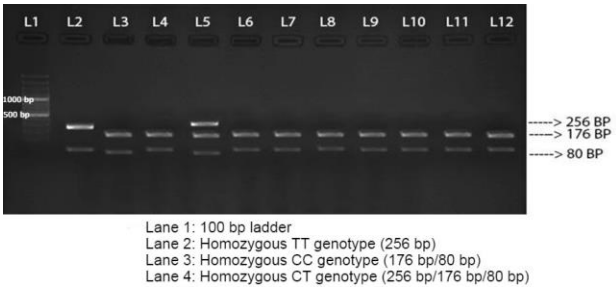

Figure 1. The image of PCR products under UV light as a result of interference with the restriction enzyme HpaII

Sequence Analysis: Following the identification of the individuals' genotypes, randomly chosen samples were sent for sequencing analysis to verify the precision of these genotypes. In Figure 2, the image of the analysis result of the gene sequences obtained from the FinchTV computer program is shown. The peaks in the base sequences obtained with the FinchTV program were carefully examined.

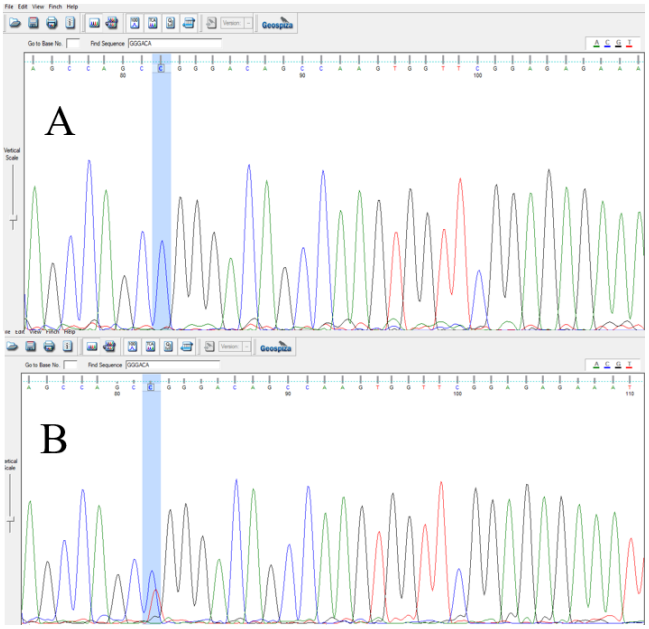

Figure 2. A) Sequence image of CC genotype, B) Sequence image of CT genotype

Statistical Data Analysis: Data analysis was done using SPSS software, version 24.0, which stands for Statistical Packages for Social Sciences. The Mann-Whitney U test and chi square test was employed for the parameters that did not fit the normal distribution criteria, whereas the t test was utilized for the values that satisfied the condition.

Results

Biochemical Results: According to the analysis results of uric acid, ALT, NA, K, WBC, HGB, and PLT parameters, it was determined that there was no significant link between T2DM patients and the control group ($p>0.05$) (Table 1).

Table 1. Comparison of study groups in terms of parameters using t test (n: number of individuals, sd: standard deviation, t: t test, p: p value)

		n	mean	sd	min	max	t	P
Age	Patient	45	57.29	15.43	-	-	**1.131**	**0.261**
	Control	52	53.96	13.56				
Uric acid	Patient	45	4.99	1.98	4	8	**0.021**	**0.983**
	Control	52	4.98	1.92				
ALT	Patient	45	30.42	20.56	5	33	**-0.573**	**0.568**
	Control	52	33.37	28.63				
Na	Patient	45	137.87	3.68	136	145	**-1.127**	**0.263**
	Control	52	138.75	3.99				
K	Patient	45	4.50	0.57	3,5	5,1	**1.869**	**0.065**
	Control	52	4.27	0.61				
WBC	Patient	45	9.16	2.86	4,3	10.3	**0.026**	**0.979**
	Control	52	9.14	3.90				
HGB	Patient	45	12.66	3.12	12	14	**-0.051**	**0.959**
	Control	52	12.69	2.44				
PLT	Patient	45	290.42	87.70	150	450	**0.374**	**0.709**
	Control	52	282.21	122.55				

There is a statistically significant difference between the control group and T2DM patients when the analytical findings of the glucose, urea, and creatinine parameters are examined ($p<0.05$). These levels are lower in the controls than in the patients when the averages of these parameters are taken into account. There was no statistically significant difference between T2DM patients and the control group in terms of GGT and amylase parameters ($p>0.05$) (Table 2).

Table 2. Comparison of study groups in terms of parameters using Mann Whitney U test (n: number of individuals, sd: standard deviation, U: Mann Whitney U test, p: p value, *: p<0.05)

		n	mean	Sd	min	Max	U	p
Glucose	Patient	45	198.47	94.84	82	115	**-7.519**	**0.000***
	Control	52	91.50	6.16				
Urea	Patient	45	47.43	28.41	17	49	**-2.198**	**0.028***
	Control	52	39.91	27.61				
Creatinine	Patient	45	1.24	1.28	0,5	0,9	**-2.532**	**0.011***
	Control	52	0.84	0.57				
GGT	Patient	45	55.44	60.11	40	80	**-1.205**	**0.228**
	Control	52	59.65	101.97				
Amylase	Patient	45	63.46	32.63	40	90	**-0.423**	**0.672**
	Control	52	71.23	74.52				

Genotype Analysis Results: The correlation between genotype and genotype frequencies in T2DM patient and control groups for the SLC30A8 gene's rs13266634 polymorphism is shown in Table 3. The genotypes of 45 people with T2DM and 52 people in the control group were determined at random. The frequency of the CC, CT, and TT genotypes in T2DM patients is 47.2%, 20.0%, and 80.0%, respectively, compared to 52.8%, 80.0%, and 20.0% in controls. The findings of the study revealed that the incidence of TT was higher in the T2DM patient group, while the incidence of CT was higher in the control group. There was no statistically significant relationship between the groups or gender ($p>0.05$).

Table 3. Genotype relationship between T2DM patients and control groups (n: number of individuals, X2: chi-square test, p: p value, *: p<0.05)

		Patient		Control		Chi-square test	
		n	**%**	**N**	**%**	X^2	**p**
Genotype	CC	34	47.2	38	52.8	**0.002**	**0.781**
	CT	3	20.0	12	80.0	**3.793**	**0.050***
	TT	8	80.0	2	20.0	**5.064**	**0.027***

The results of the study show that people with the CC genotype in the T2DM patient and control groups have statistically significant differences in glucose, urea, and creatinine levels ($p<0.05$). Furthermore, the control group's averages of these values were lower than the T2DM patient group's averages (Table 4). Other than glucose, urea, and creatinine, there is no statistically significant difference between the T2DM patient group and the control group among those with the CC genotype ($p>0.05$). The average K and PLT values in the T2DM case group are higher than in the control group. For all other parameters, it is possible to conclude that the T2DM case group had lower averages than the control group (Table 4).

Table 4. Comparison of biochemical parameters of T2DM patient group with CC genotype and control group (Ref: reference, sd: standard deviation, p: p value, a: t test, b: Mann Whitney U test, *: $p<0.05$)

	CC							
	Patient		Control		Ref. Values		Comparison Test	
	mean	**sd**	**mean**	**Sd**	**min**	**max**	**Test Statistics**	**P**
Age	56.65	15.13	52.87	13.36	-	-	**1.125[a]**	**0.264**
Uric acid	4.99	1.91	5.11	2.08	4	8	**-0.252[a]**	**0.801**
ALT	30.76	21.02	36.89	31.49	5	33	**-0959[a]**	**0.341**
Na	137.76	3.79	138.66	4.53	136	145	**-0.902[a]**	**0.37**
K	4.49	0.56	4.33	0.62	3,5	5,1	**1.119[a]**	**0.267**
WBC	9.28	2.93	9.56	4.22	4,3	10,3	**-0.317[a]**	**0.752**
HGB	12.37	3.22	12.65	2.47	12	14	**-0.422[a]**	**0.675**
PLT	276.79	82.69	274.82	125.23	150	450	**0.078[a]**	**0.938**
Glucose	204.41	102.51	91.05	6.29	82	115	**-6.263[b]**	**0.000***
Urea	48.65	28.7	41.88	31.12	17	49	**-2.147[b]**	**0.032***
Creatinine	1.36	1.43	0.81	0.63	0,5	0,9	**-3.204[b]**	**0.001***
GGT	49.88	50.4	69.97	117.26	40	80	**-0.908[b]**	**0.364**
Amylase	58.2	24.15	70.37	81.77	40	90	**-0.034[b]**	**0.973**

There is a statistically significant difference in glucose levels between people with the CT genotype in the T2DM patient and control groups ($p<0.05$). Furthermore, the mean glucose value for the T2DM patient group is higher than the mean for the control group (Table 5).

Table 5. Comparison of biochemical parameters of T2DM case group with CT genotype and control group (Ref: reference, sd: standard deviation, p: p value, a: t test, b: Mann Whitney U test, *: $p<0.05$)

	CT							
	Patient		Control		Ref. Values		Comparison Test	
	mean	**sd**	**mean**	**Sd**	**min**	**max**	**Test Statistics**	**P**
Age	48.67	17.1	55.75	15.02	-	-	**-0.715[a]**	**0.487**
Uric acid	5.67	1.91	4.57	1.5	4	8	**1.088[a]**	**0.296**
ALT	29.33	18.01	23	17.34	5	33	**0.563[a]**	**0.583**
Na	140	2	138.83	2.17	136	145	**0.844[a]**	**0.414**
K	4.67	0.23	4.18	0.6	3,5	5,1	**1.339[a]**	**0.203**
WBC	10.51	4.51	8.1	2.84	4,3	10,3	**1.183[a]**	**0.258**
HGB	14.37	2.31	12.59	2.54	12	14	**1.099[a]**	**0.292**
PLT	297	45.04	301.08	126.74	150	450	**-0.054[a]**	**0.958**
Glucose	125.67	16.01	92.08	5.2	82	115	**-2.603[b]**	**0.009***
Urea	33.53	9.88	33.17	12.63	17	49	**-0.436[b]**	**0.663**
Creatinine	0.73	0.12	0.91	0.38	0,5	0,9	**-0.443[b]**	**0.658**
GGT	19	9.85	33.33	23.68	40	80	**-1.156[b]**	**0.248**
Amylase	77.33	18.93	67.67	47.71	40	90	**-0.866[b]**	**0.386**

Other than glucose, there was no statistically significant difference between the T2DM patient group and the control group among those with the CT genotype (p>0.05). Furthermore, while the average PLT, creatinine, and GGT readings in the T2DM patient group were lower than those in the control group, the averages of the other parameters were found to be higher (Table 5).

Among people with the TT genotype, there was no statistically significant difference in parameters between the T2DM patient group and the control group (p>0.05). T2DM patients with the TT genotype have higher ALT, K, WBC, PLT, glucose, urea, and GGT levels than the control group. Aside from these measures, the averages of uric acid, Na, HGB, creatinine, and amylase levels in T2DM patients are lower than in the control group (Table 6).

Table 6: Comparison of biochemical parameters of T2DM case group with TT genotype and control group (Ref: reference, sd: standard deviation, p: p value, a: t test, b: Mann Whitney U test, *: p<0.05)

	TT							
	Patient		Control		Ref. Values		Comparison Test	
	mean	**sd**	**mean**	**sd**	**min**	**Max**	**Test Statistics**	**P**
Age	63.25	16.07	64	1.41	-	-	**-0.130[a]**	**0.900**
Uric acid	4.74	2.45	5.05	1.06	4	8	**-0.170[a]**	**0.869**
ALT	29.38	21.88	28.5	2.12	5	33	**0.054[a]**	**0.958**
Na	137.5	3.74	140	0	136	145	**-0.904[a]**	**0.393**
K	4.48	0.75	3.65	0.07	3,5	5,1	**1.483[a]**	**0.176**
WBC	8.14	1.82	7.53	0.43	4,3	10,3	**0.457[a]**	**0.660**
HGB	13.26	2.99	14	2.26	12	14	**-0.321[a]**	**0.756**
PLT	345.93	105.31	309.5	33.23	150	450	**0.464[a]**	**0.655**
Glucose	200.5	66.98	96.5	10.61	82	115	**-1.828[b]**	**0.068**
Urea	47.45	32.76	42.8	24.21	17	49	**0.000[b]**	**1.000**
Creatinine	0.95	0.57	1	0.28	0,5	0,9	**-0.793[b]**	**0.428**
GGT	92.75	91.65	21.5	12.02	40	80	**-1.306[b]**	**0.192**
Amylase	80.63	57.34	109	87.68	40	90	**-0.522[b]**	**0.602**

Discussion

The polymorphism rs13266634 was found in this study's analysis of SLC30A08 gene sequences from both the T2DM patient and control groups. When the genotypes of the patient and control groups were compared, the genotypes of the two groups showed a statistically significant correlation with the groups (p<0.05). T2DM patients had a higher prevalence of the TT genotype (80.0%) than the CT genotype (80.0%) in the control group (80.0%).

In our study, we looked at biochemical variables like glucose, urea, and creatinine, as well as the relationship between genotype and study groups. When the two groups were compared, there was a statistically significant difference (p<0.05) between the control group and the T2DM patient group. When these numbers were compared as T2DM individuals versus controls, it was discovered that glucose (198.47/91.50), urea (47.43/39.91), and creatinine (1.24/0.81) had average values and were lower in the control group. The fact that the analyses performed in our study revealed no significant association between genotype and gender adds to the credibility of our study.

Wu et al. (2008) investigated the relationship between the SLC30A8 gene and T2DM in the Chinese Han population, which included 424 people with Type 2 diabetes, 878 people with impaired fasting glucose (IFG), and 1,908 people with normal fasting glucose. In this study's sample of 3,210 people, 17 single nucleotide polymorphisms were genotyped (SNPs). The SLC30A8 gene region most likely contributes to the risk of T2DM caused by -cell dysfunction, they concluded (16).

Mtiraoui et al., on the other hand, carried out studies in

2012 on Lebanese (751/918) and Tunisian (1470/838) individuals (patients/controls) to determine the risk of SLC30A8 gene on T2DM. Both populations had different associations with the SLC30A8 gene and T2DM. This study assessed the risk of developing T2DM in Lebanese and Tunisian populations (17).

Alharbi et al. conducted a genotyping study on 120 T2DM patients and 120 control groups to determine the association between the rs13266634 genetic variant of the SLC30A8 gene and T2DM disease in the Saudi population in 2021. In their ANOVA analysis, they found no relationships between the rs13266634 genotypes or the anthropometric and biochemical parameters examined in this study. Because it produced a statistically significant difference, our study was more consistent with the literature (12).

Mashal et al. genotyped 358 T2DM patients and 326 control people in 2021 to detect increased T2DM risk and SLC30A8 (rs13266634) gene polymorphism in the Jordanian population. They discovered a link between T2DM and the SLC30A8 (rs13266634) gene polymorphism as a result of their research. This study established the effect of the SLC30A8 gene polymorphism rs13266634 on T2DM disease in the Jordanian population. This study is also supported by our findings (18).

In order to establish the link between SLC30A8 gene polymorphism and T2DM, Fan et al. conducted a meta-analysis study in 2016 with data from 46 studies involving 71,890 patients and 96,753 controls. The rs13266634 C/T polymorphism was linked to a higher risk of T2DM in the allelic frequency comparisons performed after the first pooling of the general data in the meta-analysis. The findings of the study demonstrated how SLC30A8 gene variation affects Asian, European, and African populations. Although it is seen in this study that SLC30A8 gene polymorphism is effective in different ethnic origins, the fact that the study is a meta-analysis, dealing with different populations, and having a large number of studied samples gives the study an advantage. With this study, the results of our study can be said to support each other (13).

In general, this study and the studies in the literature are consistent. This adds to the significance of our work. We believe that our findings will help determine how the rs13266634 polymorphism in the SLC30A08 gene contributes to the onset of T2DM and will serve as a model for future research. The limitation of our study is that the study samples are small and limited to a specific region. Because the sample size in our study was small, we can conclude that increasing the sample size in future studies based on the evaluation of gene polymorphisms in the development of T2DM would be more beneficial.

Declaration of Interest: Regarding the publishing of this paper, the authors affirm that there are no conflicts of interest.

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