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Association of TCF7L2 polymorphisms rs7903146 and rs4506565 with risk of type 2 diabetes mellitus in the Egyptian patients

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ABSTRACT

In the last decades, diabetes became one of the most prevalent health problems that threatens people worldwide. Diabetes is defined as a chronic metabolic disorder characterized by elevated blood glucose level (hyperglycemia) that develops as impaired of insulin function or insufficient of insulin production by the pancreas, resulting in insulin deficiency. Type 2 diabetes Mellitus (T2DM) is one type of diabetes resulting from the inability of muscle, fate, liver cells to up take glucose due to insulin resistance and incapability of pancreas to increase insulin secretion to compensate for insulin resistance. T2DM is a multifactorial disease arises from environmental factor, hereditary factor or both of them. Although there are many genes related to T2DM, the transcription factor 7-like-2 gene (TCF7L2) rs7903146 (A/T) and rs4506565 (C/T) polymorphism are two of the most susceptible genes to T2DM discovered to date, with the contribution to the disease through the Wnt/β-catenin signaling pathway affecting pancreatic islet development. This study investigates and analyze the correlation of TCF7L2 gene polymorphisms and their association with type 2 diabetes for Egyptian patients. The study included 100 blood samples equally divided into two groups: 50 patients with T2DM and 50 normal healthy controls. All Genotypes of rs7903146 (A/T) SNP in theTCF7L2 gene were evaluated by RFLP- PCR using RSA1 restriction enzyme. And all Genotypes of rs4506565 (C/T) were evaluated by ARMS-PCR. Both of them showed non-significant differences, and no association with T2DM.

***Keywords*:** Type 2 diabetes mellitus, Transcription factor 7-like-2, rs7903146 polymorphism, rs4506565 polymorphism, Egyptian patients.

INTRODUCTION:

Diabetes is a disease that is defined by a chronic state of hyperglycemia that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin and it produces uncontrolled diabetes causes hyperglycemia, or an increase in blood sugar, which over time causes significant damage to the body's systems, particularly the neurons and blood vessels (Witka *et al.*,2019). Type 2 diabetes mellitus (T2DM) represents a group of polygenic metabolic and endocrine disorders with various genetics and environmental influences that affect the capacity of the body to produce or use insulin, resulting in hyperglycemia, which may lead to variable complications. (Aboelkhair *et al*., 2021). It has become one of the foremost chronic non-communicable diseases distressing the health of people worldwide. (De Rosa *et al.*,2018). The global prevalence is increasing at a dreadful rate, making it the most dreaded silent epidemic of the twenty-first century.

According to the latest data released by the International Diabetes Federation

(IDF) (Saeedi *et al.*,2019*)* the global prevalence of diabetes reached 10.5% in 2021. Of these cases, 537 million adults live with diabetes, which is an increase of 16% (74 million) from 2019. However, nearly half (44.7%) of adults have not yet been diagnosed. The IDF predicts that by 2045, 784 million adults will have diabetes, which is more than double the estimated population (20%) over the same period (Saeedi *et al.*,2019; Sun *et al.*,2022).

The development of research and studies have led to the discovery of many genes that are related to the development of type 2 diabetes; from these genes. The transcription factor 7-like 2 genes (TCF7L2) has a significant relationship with diabetes (Grant *et al.*,2006; Guinan, 2012). And there is emerging evidence that some genetic polymorphisms can impact the risk of evolving T2DM (Sun *et al.*,2022*)*.

The TCF7L2 gene spans around 215,863 bases on the chromosome 10q25.3. The TCF7L2 codes for a transcription factor tangled in the Wnt signaling pathway, which plays an important role in adipogenesis and development of pancreatic islets. Also, TCF7L2 plays a significant role in controlling the biosynthesis, processing and secretion of insulin (Dalhat and Musa, 2018).

SUBJECTS AND METHODS

Study population:

This study was carried out in the Institute of Genetic Engineering and Biotechnology Research Institute-University of Sadat City from October 2023 until June 2024. The study included 100 blood samples of Egyptian persons, equally divided into two groups: 50 patients with T2DM and 50 normal healthy controls. Blood samples were collected from both groups for biochemical examinations and molecular study. The age of patients and normal healthy controls ranged from 25 to 80 years. Age, fasting blood glucose, glycated hemoglobin, liver function tests, kidney function tests, complete blood picture and lipid profiles were evaluated in serum specimens of T2DM patients and normal healthy controls.

Inclusion criteria: patients of T2DM and control persons.

Exclusion Criteria of T2DM were any subjects diagnosed with T1DM who are on insulin therapy and Pregnant women.

Genomic DNA Extraction and Genotyping:

Genomic DNA for genotyping was extracted from peripheral blood using DNA Blood Mini Kit (Qiagen GmbH, Germany). According to manufacturer instructions. The extracted DNA was kept at -20°C until use. TCF7L2 rs7903146 SNP was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using restriction enzyme RSAI. Genomic DNA was subjected to amplification using PCR under the following conditions: 95° C for 5 min followed by 35 cycles of 95° C for 15 s, 52° C for 15 s, 72° C for 30 s, and a final step of extension at 72° C for 10 minutes. Sequences of the primers used were as follows:

5′- TTAGAGAGCTAAGCACTTTTTAGGTA-3′(Forward),

5′- AGAGATGAAATGTAGCAGTGAAGTG -3′(Reverse).

Subsequently, 1µg of the amplified PCR product was digested with 5 units of RsaI fast digest restriction enzyme (Thermo Fisher Scientific Inc. USA) for two hours at 37 °C. Then, RFLP products were separated on a 4% agarose gel electrophoresis and visualized by Gel-Doc Imaging System (E-Box VILBER, France). After digestion, three fragments of 113, 91, and 22 bp were detected in CT genotype, 91,22 bp fragment was detected in CC genotype and finally the 113 bp fragment only was detected in TT genotype.

Another TCF7L2 rs4506565 SNP was genotyped by using modified ARMS

PCR assay (Amplification Refractory Mutation System).

Briefly, (A allele), forward (5'-ATAGAGACCCTTGACAAGGGCCCTAT-3') (T allele) forward (5'-GGATATGGCGACCGAAGTGGTT-3'), and outer F primer (5'- GTGCTCAGCATGGACTAAGGA-3'), outer R primer (5'- CTGACATGTTGCATCTCTCCATA-3')

In a modest modification of the T-ARMS PCR procedure, an outside PCR product was amplified before conducting the T-ARMS PCR. The T-ARMS PCR used this outer PCR as a DNA template. In summary, it was made up of Taq polymerase and four primers, two of which were outer primers. In a final reaction volume of 10 µl. After a 5-min preheating period at 94 ◦C, 35 cycles of denaturation were performed at 94◦C for 30 s, annealing at 56 ◦C for 30 s, extension at 72 ◦C for 60 s, and a final extension at 72 ◦C for 5 min. To score the PCR findings, they were run on 1.5% agarose gel which electrophorized at 90 volts for 40 minutes (Abdulla and Ali, 2022). The gels were stained with Ethidium Bromide. The genotypes can be differentiated by comparing amplicon sizes to molecular size markers. DNA fragments were separated by electrophoresis on a 2% agarose gel visualized with ethidium bromide and run for 45 minutes.

Product of PCR were divided into: Wild type genotype (TT) has 2 bands (432+194). Hetero genotype (TA) has 3 bands (432+287+194). Mutant Allele (AA) has 2 bands (432+287)

Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were

1. Chi-square test: For categorical variables, to compare between different groups
2. Fisher's exact test: Correction for chi-square when more than 20% of the cells have expected count less than 5
3. Student t-test: For normally distributed quantitative variables, to compare between two studied groups
4. Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups

RESULTS

The present study examined the possible relationship between T2DM and the single nucleotide polymorphisms (SNPs) at rs7903146 (C/T), and rs4506565 (A/T) in TCF7L2 gene in both of T2DM patients and the control group. Analyzing the demographic characteristics of the sample study (Table 1) reveals that there were no significant differences between both of control and diabetic persons regarding to the gender whereas $P = 0.271$. While there was a significant difference observed regarding to the age between both of the control and diabetic persons whereas (Av. Age is 49.0±11.47 years vs. 56.38±11.39 years ($p = 0.002$, significant differences achieved as $p < 0.05$).

The results of the biochemical examinations including fasting blood glucose, post prandial glucose, HBA1C, total Cholesterol, Triglycerides, AST, ALT, Urea, and Creatinine were significantly higher in patients than the healthy individuals ($p < 0.05$) (Table 2).

Table (1): Comparison between the two studied groups according to demographic Data.

	Diabetic (n = 50)		Control (n = 50)		Test of Sig.	p
	No.	%	No.	%		
Gender						
Male	33	66.0	38	76.0	χ^2= 1.214	0.271
Female	17	34.0	12	24.0		
Age (years)						
Min. – Max.	20.0 – 80.0		28.0 – 75.0		t= 3.230*	0.002*
Mean ± SD.	56.38 ± 11.39		49.0 ± 11.47			
Median (IQR)	58.50(48.0 – 65.0)		48.0 (40.0 – 58.0)			

IQR: **Inter quartile range** SD: **Standard deviation** **t: Student t-test**
p: p value for comparing between the two studied groups *: Statistically significant at $p \leq 0.05$

Table (2): Comparison between the two studied groups according to biochemical Parameters.

Parameters	Diabetic (n = 50)	Control (n = 50)	Test of Sig.	p
HBA1C				
Min – Max.	5.20 – 13.50	4.50 – 6.80	t= 8.167*	<0.001*
Mean ± SD.	7.61 ± 1.76	5.50 ± 0.49		
Median (IQR)	7.30 (6.20 – 8.30)	5.40 (5.10 – 5.70)		
ALT				
Min – Max.	21.0 – 47.0	15.0 – 40.0	t= 5.364*	<0.001*
Mean ± SD.	33.48 ± 7.52	25.92 ± 6.54		
Median (IQR)	34.0 (26.0 – 39.0)	25.0 (21.0 – 31.0)		
AST				
Min – Max.	22.0 – 46.0	20.0 – 43.0	t= 2.720*	0.008*
Mean ± SD.	34.42 ± 5.93	30.94 ± 6.84		
Median (IQR)	35.0 (29.0 – 40.0)	29.50 (25.0 – 38.0)		
Creatinine				
Min – Max.	0.60 – 1.80	0.50 – 1.60	t= 1.997*	0.049*
Mean ± SD.	1.01 ± 0.29	0.91 ± 0.24		
Median (IQR)	1.0 (0.80 – 1.20)	0.90 (0.70 – 1.0)		
Cholesterol				
Min – Max.	114.0 – 270.0	125.0 – 230.0	t= 3.984*	<0.001*
Mean ± SD.	190.0 ± 35.08	166.6 ± 22.09		
Median (IQR)	191.5 (168.0 – 214.0)	170.0 (145.0 – 181.0)		
Urea				
Min – Max.	21.0 – 60.0	20.0 – 60.0	U= 898.000*	0.015*
Mean ± SD.	35.24 ± 9.53	31.14 ± 7.96		
Median (IQR)	34.0 (28.0 – 40.0)	29.50 (26.0 – 36.0)		
FBS				
Min – Max.	74.0 – 422.0	70.0 – 118.0	U= 309.000*	<0.001*
Mean ± SD.	140.7 ± 63.76	89.50 ± 11.69		
Median (IQR)	126.5 (107.0 – 145.0)	87.50 (80.0 – 98.0)		
PPBS				
Min – Max.	98.0 – 469.0	89.0 – 172.0	U= 184.000*	<0.001*
Mean ± SD.	214.0 ± 88.20	109.3 ± 15.19		
Median (IQR)	188.0 (136.0 – 271.0)	107.5 (98.0 – 116.0)		
TG				
Min – Max.	60.0 – 240.0	74.0 – 171.0	U= 5.330*	<0.001*
Mean ± SD.	138.9 ± 41.20	104.3 ± 20.17		
Median (IQR)	134.0 (107.0 – 162.0)	103.0 (89.0 – 114.0)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test U: Mann Whitney test
p: p value for comparing between the two studied groups *: Statistically significant at $p \leq 0.05$

In addition, comparison between the control and T2DM patients shows no significant differences in hematological profile including hemoglobin, red blood cells, white blood cells, and platelets ($p > 0.05$) (Table 3).

Table (3): Comparison between the two studied groups according to CBC (Hematological profile)

Hematological parameters	Diabetic (n = 50)	Control (n = 50)	t	p
HB				
Min – Max.	8.80 – 15.10	7.0 – 15.90		
Mean ± SD.	12.73 ± 1.66	13.15 ± 1.98	1.129	0.262
Median (IQR)	12.70 (11.30 – 14.30)	13.80 (11.90 – 14.70)		
RBCs				
Min – Max.	3.60 – 6.0	3.0 – 6.30		
Mean ± SD.	5.02 ± 0.55	5.06 ± 0.75	0.350	0.727
Median (IQR)	5.0 (4.60 – 5.50)	5.05 (4.80 – 5.60)		
WBCs				
Min – Max.	3.70 – 11.70	3.90 – 11.0		
Mean ± SD.	6.79 ± 1.79	6.84 ± 1.77	0.129	0.898
Median (IQR)	6.75 (5.40 – 7.50)	6.50 (5.60 – 8.0)		
PLT				
Min – Max.	90.0 – 435.0	81.0 – 377.0		
Mean ± SD.	228.4 ± 62.75	219.1 ± 63.25	0.743	0.459
Median (IQR)	220.5 (196.0 – 259.0)	214.0 (183.0 – 246.0)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test
p: p value for comparing between the two studied groups

For rs7903146 polymorphism, the T allele frequency of the patients and control was 65.0% and 58.0% ($p = 0.254$), respectively. The respective frequency of CC, CT, and TT genotypes were 12.0, 46.0 and 42.0 % in patients, and 18.0, 48.0 and 34.0 % in control showing no significant ($p > 0.05$) (Table 4).

Table (4): Comparison between the two studied groups according to TCF7L2 rs7903146 RFLP by RSA1.

	Diabetic (n = 50)		Control (n = 50)		χ^2	p
	No.	%	No.	%		
TCF7L2 rs7903146 RFLP by RSA1						
CC	6	12.0	9	18.0		
CT	23	46.0	24	48.0	1.042	0.594
TT	21	42.0	17	34.0		
$^{HW}p_0$	0.938		0.917			
Allele						
C	35	35.0	42	42.0	1.299	0.254
T	65	65.0	58	58.0		

χ^2: Chi square test
$^{HW}p_0$: p value for Chi square for goodness of fit for Hardy-Weinberg equilibrium (If $P < 0.05$ - not consistent with HWE.) p: p value for comparing between the studied groups

For rs4506565 polymorphism, the T allele frequency of the patients and control was 40 % and 48 % (p = 0.309), respectively. The frequency of TT, TA, and AA genotype were respectively 14.0, 52.0 and 34.0 % in patients and 30.0, 36.0 and 34.0 % in control showing no significant (p > 0.05) (Table 5).

Table (5): Comparison between the two studied groups according to TCF7L2 rs4506565 ARMS.

	Diabetic (n = 50)		Control (n = 50)		χ^2	p
	No.	%	No.	%		
TCF7L2 rs4506565 ARMS						
TT	7	14.0	15	30.0		
TA	26	52.0	18	36.0	4.364	0.113
AA	17	34.0	17	34.0		
$^{HW}p_0$	0.556		0.049*			
Allele						
T	40	40.0	48	48.0	1.035	0.309
A	60	60.0	52	52.0		

χ^2: Chi square test
$^{HW}p_0$: p value for Chi square for goodness of fit for Hardy-Weinberg equilibrium (If P < 0.05 - not consistent with HWE.) p: p value for comparing between the studied groups

As a result, there were no significant differences in genotype frequencies observed between T2D patients and controls. Thus, there was no association between both of rs7903146 and rs4506565 with the risk of T2DM.

In conclusion, the current results of rs7903146 and rs4506565 did not reveal the association of this widely replicated variant of TCF7L2 gene with increased risk of T2D in Egypt populations.

DISCUSSION

Diabetes mellitus (DM) is the eighth most frequent leading cause of death around the world and its prevalence is increasing worldwide. T2DM is the most frequent type of DM (90%). Multiple genes and environmental factors affect the prevalence of T2DM (Schunkert *et al.*,2011). The TCF7L2 locus has been shown to have a considerable effect on the pathogenesis of T2DM (Palizban *et al.*,2012). TCF7L2 encodes a transcription factor involved in Wnt/β-catenin signaling pathway that regulates cell survival, cell migration, proliferation and differentiation. The overexpression of the gene in pancreatic β cells results in impaired insulin secretion. The single nucleotide polymorphisms (SNPs) in TCF7L2 gene have been studied extensively with more emphasis on rs7903146 (C/T) and rs4506565 (A/T) (Achrya *et al*., 2015).

Candidate gene association studies (CGAS) and genome wide association studies (GWAS) identified multiple genes associated with diabetes type 2. Transcription factor 7-like 2 (TCF7L2) is gang head of type 2 diabetes susceptible genes (Hattersley, 2007). Risk variants leads to over-expression of TCF7L2 gene in beta cells of pancreas but the mechanism is not fully understood and it is a question which is still need to be answered by geneticists, resulting in reducing secretion of insulin from beta cells and hence increasing blood sugar level (Loder *et al.,* 2008; Xavier *et al*., 2009).

Identification of TCF7L2 as one of the T2DM target genes in Genome Wide Association Studies (GWAS) and case-control studies (Mccarthy and Zeggini, 2009) has lead researchers to study the gene extensively for various SNPs correlating to the manifestation of hyperglycemia. As a result, SNPs in various loci of TCF7L2 have been shown to be associated with T2DM among many populations of various ethnicity and geographical locations (Nemr *et al*., 2012; Chandak *et al*., 2007; Turki *et al*., 2013). However, there has been a contrasting report showing weak or lack of association between TCF7L2 common variants rs7903146 and rs4506565 and T2DM in Arab populations (AL-Smadi *et al*., 2008)

The current study of the SNPs in TCF7L2 gene and its correlation with T2DM recorded no association of rs7903146, and rs4506565 variant with T2DM risk in the Egyptian populations, whereas no significant differences in genotype frequencies were observed between T2DM patients and controls. Also, the T allele frequency for rs7903146 polymorphism of the patients and control was 65.0% and 58.0% ($p = 0.254$) respectively. The frequency of CC, CT, and TT genotypes were respectively 12.0 %, 46.0 %, and 42.0% in patients, and 18.0 %, 48.0 %, and 34.0 % in control show no significant ($p > 0.05$).

This study reveals that rs7903146 failed to demonstrate any correlation for the same population group. The minor T allele frequency for the SNP rs7903146 among the Egyptian population showed no statistically significant difference ($p = 0.254$).

Results of this study concerning the allelic distribution of the TCF7L2 rs7903146(C/T) polymorphism came to agreement with studies performed on Arab Caucasians in Saudi Arabia by Acharya *et al*. (2015), as well as in the United Arab Emirates by Saadi *et al.* (2008), whose results showed no significant association of the SNP with T2DM. In addition, another study conducted among Africans in Cameroon by Guewo-Fokeng *et al*. (2015) showed that there was no association of the SNP with T2DM. Similar results were obtained in studies carried out by Pourahmadi *et al*. (2015) in Iran and Chang *et al.* (2007) in China, where the T allele was not found to have an impact on the association with T2DM.

Moreover, the results of the present study agreed with results of another study conducted on Saudi Arabia populations which showing weak or lack of association between TCF7L2 common variants rs7903146 and T2DM (Achrya *et al.,* 2015). However, in contrast to the present study, other studies replicated in European, Asian, African, and Caucasian ethnicities concluded that the presence of the T allele was associated with increased risk of T2DM. For instance, regarding European ancestry, González-Sánchez *et al*. (2008) conducted a study in Spanish population and found a statistical significance of the occurrence of the T allele with T2DM. Anjum *et al.* (2018) in Chinese population, Danquah *et al.* (2013) in Ghanaian population, Ezzidi *et al.* (2009) in Tunisian population, and Assmann *et al.* (2014) in Brazilian population came to the same conclusion of the significance of association of the TCF7L2 rs7903146 (C/T) polymorphism and T2DM susceptibility, especially the homozygous TT genotype. A meta-analysis conducted by Lou and Wang (2019) and Ding *et al.* (2018) on subjects from different ethnic groups showed a positive correlation of the rs7903146 C/T SNP with T2DM.

In the current investigation the T allele frequency of the patients and control for rs4506565 polymorphism was 40 and 48%, respectively. The respective frequency of TT, TA, and AA genotype were 14.0, 52.0

and 34.0 % in patients and 30.0, 36.0 and 34.0 % in control showing no significant association with the risk of T2DM. This finding agrees with the results of the meta-analysis conducted by Sihu *et al.* (2013) where the subgroup analysis revealed that the significant association were not found between the SNP rs4506565 and T2DM in some ethnic populations.

However, TCF7L2 SNP rs4506565 had earlier been documented to be associated with T2DM with a varying degree among Lebanese (Nemr *et al*., 2012), Tunisian Arabs (Turki *et al.*,2013), and Saudi Population (Acharya *et al*., 2015). In addition, a meta-analysis conducted by Xin and Jinhui (2021) proved that TCF7L2 rs4506565, rs7901695, rs11196205 and rs12255372 polymorphisms were all significantly associated with altered susceptibility to T2DM in both Asians and Caucasians. These results supported that these polymorphisms could be used to identify individuals at high risk of developing T2DM. The current study agrees with Bahaaeldin *et al*. (2020) that the underlying mechanisms of action of TCF7L2 variants in the etiology of T2DM are still uncertain.

Conclusion:

Results of this study for TCF7L2 polymorphisms, rs7903146 and rs4506565, and their association with the risk of type 2 diabetes has not been confirmed. However, further studies with larger sample sizes are still needed to verify the current findings.

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Association of TCF7L2 polymorphisms rs7903146 and rs4506565 with risk of type 2 diabetes mellitus in the Egyptian patients

الارتباط بين جين TCF7L2 بطفرتيه rs7903146 ، rs4506565 **مع خطر الإصابة بداء السكري من النوع 2 في المرضى المصريين**

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المستخلص

لقد اصبح مرض السكرى فى العقود الاخيرة أحد أكثر المشاكل الصحية انتشارا والتى تهدد حياة الناس فى جميع انحاء العالم, حيث يعرف مرض السكرى بانه مرض مزمن ينتج من اضطراب فى عملية أيض الكربوهيدرات اى الهدم والبناء ,مما يؤدى الى ارتفاع مستوى الجلوكوز فى الدم وذلك بسبب عجز البنكرياس عن افراز كمية كافية من هرمون الانسولين او عدم استجابة الخلايا الدهنية والكبد والعضلات لهرمون الأنسولين المسئول عن تنظيم مستوى الجلوكوز فى الدم. ويعتبر داء السكرى من النوع الثانى احد انواع مرض السكرى الناتجة من عدة عوامل مثل :العوامل البيئية او العوامل الوراثية او كليهما والتى تتسبب فى خطر الاصابة بمرض السكرى. هناك العديد من الجينات التى تزيد من احتمالية خطر الإصابة بمرض السكرى ,وتهدف هذه الدراسة لاختبار العلاقة بين جين TCF7L2 بطفرتيه rs7903146، rs4506565 واحتمالية خطر الاصابة بمرض السكرى من النوع 2 فى المرضى المصريين . ولتفسير هذه العلاقة تم تطبيق هذه الفرضية على عدد 100 فرد من المصريين ,حيث تم تقسيمهم الى 50 فرد من مرضى السكرى النوع الثانى و50 فرد من الاصحاء كعناصر تحكم . حيث اشارت نتائج هذه الدراسة بأنه لايوجد ارتباط بين تعدد الاشكال الجينية لجين TCF7L2 وخطر الاصابة بمرض السكرى النوع الثانى بين المرضى المصريين.

الكلمات المفتاحية: مرض السكري من النوع الثاني. جين CF7L2 ، الشكل الجينى rs7903146 ،الشكل الجينى rs4506565. المرضى المصريين.