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Association of Insulin Growth Factor 2 Binding Protein 2 Gene rs4402960 Polymorphism with Type 2 Diabetes Mellitus in A Sample from Egyptian Patients

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Abstract

Background: Genetic variation at the insulin growth factor 2 binding protein 2 (IGF2BP2) gene has been associated with Type 2 Diabetes (T2DM) by genome-wide association studies.

Aim of Study: To assess the genetic association of insulin growth factor 2 binding protein 2 (IGF2BP2) rs4402960 polymorphism with the development of type 2 diabetes mellitus in a sample from Egyptian patients.

Patients and Methods: 50 subjects; 30 T_2DM patients and 20 healthy controls. They were subjected to: History, clinical examination, measuring glycosylated hemoglobin, lipid profile and genotyping of IGF2BP2 (rs4402960) using Taqman-based allelic discrimination technique by Real-Time PCR.

Results: There was significant statistical difference regarding allele frequency of IGF2BP2 (rs4402960) as it exhibited an increased T allele frequency in the diabetic group while G allele was decreased compared to controls. The allelic association analysis confirmed a significant association with T_2DM [OR=7.43, p=<0.001]. The frequency of (G/T + T/T) genotypes vs. G/G was significantly higher in T_2DM patients than in controls [p=0.022, OR=0.26].

Conclusion: IGF2BP2 rs4402960 was significantly associated with increased risk of T_2DM and can be used to predict the disease in Egyptian patients, and it is recommended to do this study on a large scale to confirm this association.

Key Words: *Genome-wide association – IGF$_2$BP$_2$ – Type 2 diabetes mellitus – Real-Time PCR.*

Introduction

DIABETES mellitus defined as a chronic, progressive metabolic condition mostly characterized by hyperglycemia. The commonest reasons which contribute to the pathophysiology of T_2DM are impaired insulin secretion, insulin resistance, or a combination of both [1]. Type 2 diabetes mellitus (T_2DM) is a polygenic disorder which caused by a complex interaction between environmental and genetic factors [2]. By the year 2030, there will be 8.6 million adults with diabetes in Egypt, making it the country with the tenth largest population of diabetics in the world [3]. Over the past several years, the Genome-Wide Association Studies (GWAS) have identified approximately 40 susceptibility loci which play roles in insulin secretion and pancreatic β-cell function [4]. Insulin-like growth factor 2 (IGF2) is a growth-promoting polypeptide. It shares a high degree of structural homology with insulin [5].

IGF2 has a role in glucose homeostasis through increasing peripheral glucose uptake in different tissues and inhibition of hepatic gluconeogenesis and lipolysis [6]. The functions of Insulin-like growth factor 2 is binding to the 5'-UTR of the Insulin-like Growth Factor 2 (IGF) mRNA, it is stated to be involved in growth, development, cell differentiation and metabolism [7]. Insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) belongs to a family of IGF2 mRNA-binding proteins which implicated in mRNA localization, turnover, and IGF2 translational regulation [8]. IGF2BP2 gene located on chromosome 3q27.2 [9]. IGF2BP2 has shown conflicting results regarding the nature of its association with T_2DM, particularly the SNP of this gene rs4402960 that was analyzed in different populations and yielded both strong [10,11]. As well as weak or no association [12].

Due to the disparity of results among different populations, we aimed at studying such association in Egyptian populations having T_2DM. This study was designed to assess the genetic association of insulin growth factor 2 binding protein 2 (IGF2BP2)

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polymorphism (rs4402960) with type 2 diabetes mellitus (T2DM) among Egyptian populations.

Patients and Methods

This is a cross-sectional controlled study conducted at Endocrinology Outpatient Clinic in Benha University Hospitals during the period from December 2016 to June 2017. Two groups of subjects were enrolled; group 1 (diabetic group) included 30 patients with type 2 diabetes mellitus their diagnosis was based on their medical records and fulfilling the diagnostic criteria of American Diabetes Association that specifies any of the Following Fasting Plasma Glucose (FPG) ≥ 126mg/dl or 2h Post-Prandial Plasma Glucose (PPG) ≥ 200mg/dl or random plasma glucose (Random Blood Sugar) (RBS) ≥ 200mg/dl or hemoglobin A1c (HbA1c) level ≥ 6.5% **[13]**. Group 2 (control group) included 20 healthy control subjects without personal or family history of DM. Inclusion criteria for group 1: Diabetic patient's age between 35-60 years, patient's body mass index is up to 30Kg/m^2. Exclusion criteria for group 1: Other types of diabetes (including T1DM, or Maturity-Onset Diabetes of the Young [MODY]), renal disease, hepatic disease, endocrinal disease and metabolic disorders. The study gained approval from the Ethical Committee of the Faculty of Medicine, Benha University. Informed written consent was obtained from all subjects after fully informed about all study procedures.

Methods:

- All subjects were subjected to full history taking and physical examination including; Body Mass Index (BMI) that was calculated as weight/height^2 (kg/m^2).
- Peripheral blood samples (7ml) were collected for routine workup, including Complete Blood Count (CBC), glycosylated hemoglobin (HbA1c) (%), blood glucose level (fasting and 2 hours post prandial) (mg/dl) and Lipid profile (mg/dl).
- IGF2BP2 SNP genotyping.

Genomic DNA was isolated from 200∝l EDTA blood using blood genome DNA extraction kits (G-spinTM total DNA Extraction Kit 50 columns (cat No 17045) (lot NO 15250849) INtRON Biotechnology according to the manufacturer's protocol. IGF2BP2 rs4402960 polymorphism genotyping was performed by TaqMan-based allelic discrimination method using Step One TMReal Time PCR (Applied Biosystem, Thermal Cycling Block S/N (271003648), Foster City, California, USA). All primers and probe were designed by Applied Biosystem (Foster City, CA). The following primer pairs were used:

Forward primer:

5 tGGAGCAGTAAGGTAGGATGGACAGT AGATT-3 t.

Reverse primer:

AAGATACTGATTGTGTTTGCAAACAT-GCCC-3 t.

VIC/FAM probe sequence:

5t-AGTAAGGTAGGATGGACAGTAGATT-3t.

The PCR Master Mix Kit (2X) (Cat. No. 25341/25342) contained Real MOD TMReal-time PCR solution (1ml). The real-time cycler conditions were; initial denaturation 5min, 95ºC, cycling (40 cycles: Denaturation, 5sec, 95ºC and Denaturation/Annealing, 34sec, 60ºC). Detection of SNP (G/T) Genotyping: As each SNP genotyping allele labeled with specific taqMan probe one labeled by (VIC) dye which represents allele 1 sequence for (T) typing, and another by (fam) dye which represents allele 2 sequence for (G) typing. The analysis is taken from the endpoint read of fluorescence.

Statistical analysis:

Data were tabulated, coded then analyzed using the STATA version 11 (STATA Corporation, College Station, Texas). Quantitative data were presented as mean ± SD. Student *t*-test was used to compare two groups. Pearson's correlation coefficient was used to test the correlation between variables and Chi-square test was used to compare the frequency of qualitative variables among the different groups. The Odd's Ratio (OR) and 95% Confidence Interval (95% CI) were for risk estimation. The level of significance was set at $p<0.05$.

Results

The clinical data of studied groups were shown in (Table 1). There was no significant difference between studied groups except for significant increased positive family history, BMI, SBP and DBP as they were higher in the diabetic group ($p<0.001$). Regarding laboratory data, there was a statistical significant difference between studied groups regarding their FBS, PPS, HBA1C% and lipid profile (TG, TC, HDL-C, LDL-C) as it was higher in the diabetic group ($p<0.001$) (Table 2).

Regarding genotype, the T allele frequency was significantly higher in T2DM patients than in controls ($p<0.001$), with G/G genotype, was the most frequent in controls (60%). The frequency of

(G/T + T/T) genotypes vs. G/G genotype was significantly higher in T2DM patients than in control (83.33% vs. 16.76% in patients and 40% vs. 60% in controls, respectively). (GG, TT, GG + GT, and TT) there was a statistically significant difference between studied groups as it was higher in the diabetic group while GG was lower, but there was no a statistical significant difference between studied groups regarding genotype (GT). G allele is protective but T allele is an independent risk factor for T2DM (Table 3).

Association between the different genotype groups (GG, TT, GT) of IGF2BP2 polymorphisms and sex, age, BMI, SBP, DBP, HbA_1c%, serum lipid levels, FBG, PPBG, CBC, liver function, kidney function, age of onset, duration and complication of diabetes showed that there were no significant statistical differences between them.

Multiple logistic regressions were developed to identify significant predictors for T2DM conditioned on genotype and other risk factors demonstrated that T2DM was associated TT genotype (OR; 95% CI: 38.0; 2.50 to 576.49 and p=0.009). High BMI was associated with increased risk of T2DM (3.46; 1.53 to 7.83 and p=0.003) (Table 4).

Table (1): Comparisons between studied groups regarding their socio-demographic characteristics and their clinical data.

Variable	Diabetic group (no.=30)		Control group (no.=20)		Test	p
	No.	%	No.	%		
Sex:						
Female	15	50.0	8	40.0	χ^2=	0.49
Male	15	50.0	12	60.0	0.48	
Age (ye ars):						
Mean ±SD;	49.65±7.35;		51.55±3.52;		*t*=	0.29
(Range)	(33-60)		(46-57)		1.07	
Family history:						
Negative	12	40.0	20	100.0	χ^2=	<0.001
Positive	18	60.0	0	0.0	18.75	(HS)
Consanguinity:						
Negative	21	70.0	14	70.0	χ^2=	1.00
Positive	9	30.0	6	30.0	0.00	
SBP (mm Hg):						
Mean ±SD;	130.5±15.5;		120.75±7.83;		*t*=	0.01
(Range)	(110-200)		(110-135)		2.59	(S)
DBP (mmHg):						
Mean ±SD;	85.5±7.23;		73.25±5.68;		*t*=	<0.001
(Range)	(70-100)		(60-80)		6.37	(HS)
BMI (kg/m^2):						
Mean ±SD;	28.3±1.61;		24.85±2.18;		*t*=	<0.001
(Range)	(25-30.5)		(19-28)		6.36	(HS)

p : Probability.
χ^2 : Chi-square test.
t : Student *t*-test.
S : Significant (p<0.05).
HS : Highly Significant (p<0.001).
BMI : Body Mass Index.
SBP : Systolic Blood Pressure.
DBP : Diastolic Blood Pressure.

Table (2): Comparisons between studied groups regarding their laboratory data.

Variable	Diabetic group (no.=30)	Control group (no.=20)	Test	p
FBS (mg/dl):			Mann-Whitney test=5.23	<0.001 (HS)
Mean ± SD; (Range)	128.47±39.78; (85-287)	86.05±8.92; (70-100)		
PBS (mg/dl):				
Mean ± SD; (Range)	260.2±72.72; (120-393)	153±28.22; (100-199)	6.27	<0.001 (HS)
HBA1C%:				
Mean ± SD; (Range)	7.36±0.68; (6-8.8)	5.03±0.46; (4.5-6.5)	13.35	<0.001 (HS)
TG (mg/dl):				
Mean ± SD; (Range)	166.53±68.17; (60-360)	77.85±14.32; (55-107)	5.71	<0.001 (HS)
TC (mg/dl):				
Mean ± SD; (Range)	212±34.05; (145-300)	167.21±22.08; (116-214)	5.08	<0.001 (HS)
HDL-C (mg/dl):				
Mean ± SD; (Range)	45.63±9.31; (20.5-62)	47.3±9.6; (31-67)	0.61	0.54
LDL-C (mg/dl):				
Mean ± SD; (Range)	127.79±26.61; (75-179.9)	102.93±19.33; (71.4-143)	3.59	<0.001 (HS)

p : Probability.
χ^2 : Chi-square test.
t : Student *t*-test.
S : Significant (p<0.05).
HS : Highly Significant (p<0.001).
FBS : Fasting Blood Sugar.
PPS : Post-Prandial Sugar.
HBA1C% : Glycosylated Hemoglobin.
TG : Triglycerides.
TC : Total Cholesterol.
HDL-C : High-Density Lipoproteins.
LDL-C : Low-Density Lipoproteins.

Table (3): Comparison between studied groups regarding their genotype and frequency of each allele of IGF2BP2 gene polymorphism.

IGF2BP2 polymorphisms	Cases (no.=30)		Controls (no.=20)		Chi-square test	p	OR (95%CI)
	No.	%	No.	%			
• GG	5	16.67	12	60.0	14.97	• 0.001 (S)	• 1.00
• GT	9	30.0	7	35.0	2.43	• 0.12	• 3.08 (0.6 to 16.65)
• TT	16	53.33	1	5.00	15.07	• <0.001 (HS)	• 38.4 (3.52 to 1739.68)
• GG + GT	14	46.67	19	95.0	12.49	• <0.001 (HS)	• 21.71 (2.60 to 957.14)
• TT	16	53.33	1	5.00			
• TT + GT	25	83.33	8	40.0	10.04	• 0.002 (S)	• 7.5 (1.72 to 34.86)
• GG	5	16.67	12	60.0			
• G	19/60	31.67	31/40	77.50	20.17	• <0.001 (HS)	• 7.43 (2.73 to 21.03)
• T	41/60	68.33	9/40	22.5			

p : Probability.
OR : Odd Ratio.
95% CI : 95% Confidence Interval.
S : Significant (p<0.05).
HS : Highly Significant (p<0.001).

Table (4): Multiple logistic regressions for T2DM conditioned on genotype and other risk factors to identify significant predictors.

Variable	Recessive model (TT vs. GT + GG) (no.=50)		Dominant model (TT vs. GG) (no.=34)		Additive model (T vs. G) (no.=100)	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
IGF2BP2 polymorphisms	38.0 (250 to 576.49)	0.009	8.54 (1.49 to 49.02)	0.016	11.01 (2.69 to 45.11)	0.001
BMI (kg/m^2)	3.46 (1.53 to 7.83)	0.003	3.73 (1.19 to 11.68)	0.024	3.04 (1.9 to 4.86)	<0.001

Discussion

Insulin-like growth factor 2 mRNA-binding protein 2 (IGF_2BP_2) has a role in the stimulation of insulin action. Polymorphisms in the IGF_2BP_2 gene have been analyzed in various studies to assess association of these variants with the type 2 diabetes (T2DM), but results are conflicting [14]. Our study show that there was a statistically significant difference between studied groups regarding genotype (GG, TT, GG + GT, and TT) as it was higher in the diabetic group while GG was lower, also allele T was higher in the diabetic group. These results were in accordance with a study done by El-Lebedy et al., who stated that the variant T allele was associated with T2DM as it was higher in T2DM patients than in controls (p<0.001), with G/G genotype, was the most frequent in control subjects (62.5%). The frequency of (G/T + T/T) genotypes vs. G/G genotype was significantly higher in T2DM patients (62.5%) vs. 34.5% than in controls (37.5%) vs. 62.5%, (p= 0.00001) [15].

Huang et al., found that the pooled ORs of the allele (T vs. G) of rs4402960 polymorphic loci in IGF_2BP_2 was a significant association with T2DM (OR=1.163 95%CI = [1.138, 1.189] p<0.00001) [16].

These results were also consistent with previous finding of Rao et al., who reported that the carriers of TT genotype at rs4402960 had a higher T2DM risk than the G carriers (TG + GG) (95% confidence interval (95% CI)=1.065-3.612, p=0.031] [17].

The study of Benrahma et al., demonstrated that the genotypic distribution of the rs4402960 polymorphism in IGF_2BP_2 showed that the homozygous GG genotype was 32.58%, the heterozygous GT genotype 45.25%, and the recessive homozygous TT 22.17%, in the patient group, while in the control group, genotype frequencies were 36.40% GG, 51.88% GT, and 11.72% TT. The statistical analysis showed that both the additive (OR 2.33, 95% CI 1.31-4.14; p=0.004) and recessive (OR 2.23, 95% CI 1.33-3.73; p=0.002 (models of rs4402960 polymorphism was significantly associated with diabetes. The frequency of the T allele was 37.66% and the G allele was 62.34% in the controls. A comparison of these frequencies to those observed in the patient group (T 47.8% and G 55.20%) revealed that the T allele was associated with susceptibility to diabetes (OR 1.34, 95% CI 1.032-1.74; p=0.027) [18].

On the other hand, a study performed by. Kommoju et al., reported that the allele and genotype frequencies were similar between cases and controls, for SNP of IGF_2BP_2 rs4402960. Multiple logistic regressions did not reveal significant allelic or genotypic association of this SNP with T2DM [19].

Wu et al., found that IGF_2BP_2 (rs4402960) rs4402960 was not significantly associated with T2DM and it had a protective effect against type 2 DM in obese subjects [20].

In the present study, there were no significant statistical differences between the different genotype groups regarding sex, age, SBP, DBP, HBA_1C%, serum lipid levels, FBG, PPBG, CBC, liver function, kidney function, an age of onset, duration and complication of diabetes.

These results were in agreement with Rodriguez et al., who showed that no significant association was found between hypertension status or serum lipid levels among genotype subgroups. (p>0.05 for all) [21].

However, there was a conflicted finding as Rao et al., demonstrated that there was significant associations were identified for rs4402960 in all gene of cases, regarding there diagnostic criterion, sample size, sex, average age and BMI [17]. Also, El-Lebeedy et al., showed a significant association with T2DM regarding the covariates gender, BMI, TGs, and HDL-c [15].

Multiple Logistic Regressions (MLR) were developed to identify significant predictors for T2DM conditioned on genotype and other risk factors demonstrated that T2DM was associated TT genotype (OR; 95% CI: 38.0; 2.50 to 576.49 and p=0.009). High BMI was associated with

increased risk of T_2DM (3.46; 1.53 to 7.83 and p=0.003).

Wu et al., agreed with our results by multiple logistic regressions models which were developed to demonstrate that obesity (BMI $\geq$28.0kg/m^2) remained an independent risk factor for T_2DM after potential confounder adjustment (p<0.05). While rs4402960 alone was not significantly associated with T_2DM. Both BMI and SNP rs4402960 which were detected in MLR models only confirmed a significant association between this SNP and T_2DM in the high-BMI group (p=0.008 for allele analysis and p<0.001 for genotype analysis) **[20]**.

Ruchat et al., stated that IGF2BP2 had a possible role in insulin resistance as he was found that the associations between the variant of IGF2BP2 and abdominal/visceral total fat were evidenced in Canadian Caucasians. According to this finding IGF2BP2 (rs4402960) may disturb T_2DM susceptibility through its contribution to insulin resistance, which is experienced mainly by the obese individual **[22]**.

Kargun et al., found no statistically significant difference between morbidly obese persons and non-obese individuals in terms of IGF2BP2 gene rs4402960 gene polymorphism and it's allele frequencies this may be due to a small size of samples which included in the study **[23]**.

Conclusion:

The IGF2BP2 gene rs4402960 polymorphism was found to be significantly associated with increased risk of type 2 diabetes mellitus and can be used to predict the disease in Egyptian patients, and it is recommended to do this study on a large scale to confirm this association.

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الإرتباط الجينى لتعدد الآشكال رس ٤٤٠٢٩٦٠ المعبر عن عامل النمو الذى يشبه الآنسولين ٢ بروتين ٢ مع مرض السكر من النوع الثانى فى عينة من المرضى المصريين

الهدف من البحث: تقييم الإرتباط الجينى لتعدد الآشكال رس ٤٤٠٢٩٦٠ المعبر عن عامل النمو الذى يشبه الآنسولين ٢ بروتين ٢ مع مرض السكر من النوع الثانى فى عينة من المرضى المصريين.

المرضى وطرق البحث: تمت هذه الدراسة على ٥٠ شخصا من الجنسين وتم تصنيفهم إلى مجموعة الدراسة: عددهم ٣٠ مريضا مصابا بمرض السكر من النوع الثانى. المجموعة الضابطة: عددهم ٢٠ شخصا صحيحا وتم إخضاع جميع المرضى والمجموعة الضابطة إلى:

- آخذ التاريخ المرضى والفحص السريرى الدقيق وقياس نسبة الهيموجلوبين السكرى، قياس مستوى الدهون، وعمل تفاعل البلمرة المتسلسل الكمى لعمل التحليل الخاص بالنمط الجينى رس ٤٤٠٢٩٦٠ المعبر عن عامل النمو الذى يشبه الآنسولين ٢ بروتين ٢.

النتائج: توصل البحث إلى وجود إرتباط ذو دلالة إحصائية بين المتغير الجينى المعبر عن بروتين ٢ الممثل لعامل النمو الذى يشبه الآنسولين ٢ (رس–٤٤٠٢٩٦٠) ومرض السكر من النوع الثانى حيث وجد آن هناك فروق ذات دلالة إحصائية بين مجموعات الدراسة فيما يتعلق بالصبغة الوراثية المتضادة الصفات (ت) حيث كانت آعلى فى مجموعة مرضى السكر من النوع الثانى بينما الصبغة الوراثية المتضادة الصفات (غ) كانت آقل مقارنة بالمجموعة الضابطة.

الإستنتاج: ويمكن الإستنتاج آن تعدد آشكال الجين المعبر عن عامل النمو الذى يشبه الآنسولين ٢ بروتين ٢ (رس–٤٤٠٢٩٦٠) ترتبط بشكل كبير مع زيادة خطر مرض السكر من النوع الثانى ويمكن إستخدامه للتنبؤ بالمرض بين المصريين. وينصح آن تفعل هذه الدراسة على نطاق واسع لتآكيد هذا الإرتباط.