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Insulin-like Growth Factor-2 Binding Protein-2 Gene Polymorphisms in Iraqi Patients with Type 2 Diabetes Mellitus

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Abstract

BACKGROUND: Type 2 diabetes mellitus (T2DM) represents a hyperglycemia causing metabolic disease which exists in the peripheral tissues due to insufficient insulin secretion or insulin resistance. Genetic association researches had suggested that the single-nucleotide polymorphisms (SNPs) spanning IGF2BP2 gene are associated with the progression as well as development of the T2DM.

AIM: This study aims to evaluate the association of IGF2BP2 gene polymorphisms (rs4402960 and rs1470579) with T2DM in a sample of Iraqi individuals.

METHODS: A case–control study has been conducted on 800 participants, they were divided into two equal groups, which are a healthy control group (400) and type 2 diabetic patients (400). Fasting blood sugar (FBS), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and HbA1c were measured for both participant groups. IGF2BP2 gene was genotyped for polymorphisms; rs4402960 and rs1470579 using the PCR-RFLP technique.

RESULTS: The SNP rs4402960 minor allele frequency of T allele was considerably different between the two participating groups with 33.6% in T2DM group. Homovariant TT shows a significant odds ratio (4.5) as codominant type. The rs1470579 SNP shows a significant risk (1.28) of C allele in the patients group than in A allele. The CC genotype in codominant and recessive models shows significant odds ratio differences (2.03 and 1.96), respectively. The rs1470579 SNP exerts significant differences as codominant model in biochemical features of BMI, fasting blood glucose, insulin, and HOMA-IR. The study power of rs4402960 is 69.5% and rs1470579 is 34.1%.

CONCLUSION: This study confirmed the association of rs4402960 as codominant, dominant, and recessive with T2DM significantly. However, rs1470579 is associated as recessive model with T2DM in Iraqi population.

Introduction

Type 2 diabetes mellitus (T2DM) continues to be among the world's biggest health problems, it is a hyperglycemia causing metabolic disease that exists in peripheral tissues due to insufficient pancreatic insulin secretion and/or insulin resistance [1].

Although T2DM's etiology is complex and requires more research, genetic factors have been identified as a major cause and were identified in recent years by an increasing number of candidate genes. The investigation of candidate genes that have been implicated in initiation and progression of T2DM will also be shedding the light on fundamental molecular mechanisms of this disease [2].

The IGF2 mRNA-binding protein 2 (IGF2BP-2) can be described as a member of insulin-like growth factor 2 mRNA-binding protein family. IGF2BP2 is a protein that is involved in the embryogenesis as well as the pancreatic development [3]. It is found on chromosome 3q27. IGF2BP2 can also regulate IGF2 transcription, which is crucial in insulin action development [4].

The full-length human IGF2BP2 protein is 66 kDa and has 599 amino acid types; nonetheless, splice variant p-62 is created through skipping exon 10 [5]. The two versions have tandem RNA-recognition motif tandem repeats at N-terminus and heterogeneous nuclear ribonucleoprotein K-homology domains at the C-terminus [6]. Motifs of RNA-recognition and the K-homology domains are collaborating for mediating highly precise and affinitive IGF2BP2 interactions with hundreds of the target transcripts, with varying binding preferences to RNA sequences [7].

The stability, translation, and localization of transcripts are all dependent on this relationship [8]. The IGF2BP2 was found to transport the target m-RNAs to the surface of the mitochondria and inhibiting it prevents assembly and activation of the respiratory complexes I and IV in mitochondria [9], [10]. The functional role of the IGF2BP2 in mitochondrial assemblies, metabolism, and activity is supported by some studies [11], [12]. IGF2BP2 is necessary for the development of the embryos and neuronal differentiations at the physiological level. IGF2BP2 dysregulation causes a range of illnesses, including T2DM [13].

The genetic association researches had suggested that SNPs spanning IGF2BP2 gene have been linked to the progression and development of the T2DM [13], [14]. The rs1470579 A/C, rs4402960 G/T, and rs11705701 G/A are three SNPs that are already linked to susceptibility of T2DM in various races [15], [16]. The most commonly examined variation in the IGF2BP2 gene is the rs-4402960 that was explored in a variety of the populations with mixed results [17], [18], [19]. For the two commonly investigated polymorphisms of the IFG2BP2, rs-4402960 and rs-1470579, Wu *et al.* completed the most detailed meta-analysis of 35 researches, including 175965 individuals. IGF2BP2 polymorphisms were found strongly related to an elevated incidence of T2D in a prior study, notably in the Caucasian as well as the East Asian populations [20]. Therefore, we studied these two SNPs of IGF2BP2 gene in Iraqi diabetes.

Materials and Methods

Subjects

The research project was approved by Medical Ethics Committee of Faculty of Medicine in University of Kufa. All participants signed a written informed consent. This study includes 400 T2DM cases diagnosed in Al-Najaf Center for Diabetes and Endocrinology in Al-Sader Medical City according to the American Diabetes Association measures [21]. In addition, 400 apparently healthy individuals were enrolled as the control group without signs or symptoms of diabetes also they were confirmed by investigations such as fasting blood glucose (FBG) and HbA1c. Individuals with liver, heart, renal, and malignant diseases or with insulin injection treatment excluded from the study. The biochemical parameters (which include the FBS, TG, TC, HDL-C, LDL-C, and HbA1c) measured suitable for both participant groups.

Sample collection and analyses of the biochemical markers

A 5 mL of venous whole blood were obtained from T2DM patients and control groups at fasting (between 7:00 pm and 9:00 am). Using commercially offered kits (BIOLABO, France), the biochemical parameters which include the FBS, TG, TC, HDL-C, LDL-C, and HbA1c were measured for participants of the two groups. Parameters of anthropometry as height (meter) and weight (kg) were obtained by regularized methods for the estimation of BMI for the two participants groups which were done by dividing the weight by squared height (kg/m^2).

The insulin measures by sandwich ELISA using Eagle Biosciences USA kit (cat. INS31-K01). The insulin resistance computed using homeostatic model calculation (HOMA-IR) as suggested by Matthews *et al.* [22]. HOMA-IR = [FSG(mg/dL)xFSI(μU/mL)]/405.

Extraction and genotyping of the DNA

Genomic DNA was obtained from whole-blood samples using the *Quick-gDNA™* Blood Miniprep kit (cat. D3072 & D3073). The extracted DNA's quality and amount were determined with the use of the spectrophotometric A-260/280 ratio and electrophoresis, respectively. Restriction fragment length polymorphism (RFLP) is a technique used for PCR approach. Primers have been designed using PRIMER-1 tool (found in www.primer1.soton.ac.uk/primer1.html). The designed primers' sequence of rs1470579 A>C was forward A T G G C T A C T G C A A C T A A G A C C and reverse T A T G G A C A C T G A A G G T C A A A. The rs4402960 G>T forward primer is T C T G G G C C T G G T G T C A A A G and reverse primer A G C C C G G G T C T C T A G G A T C T. The PCR reaction included 100 ng (1 μL) of the DNA, 1.0 μL of each primer (10 pm/μL), 15 μL of 2× red PCR Master Mix (Amplicon), and 2 μL of the sterile distilled water in 20 μL mix. The conditions of PCR have been as follows: Initial denaturation for 5 min at a temperature of 95°C, 35 cycles, every one of which included the denaturation at a temperature of 95°C for 30 s, annealing (rs1470579 = 59.5°C and rs4402960 = 62.5°C) for 30 s, and extension at a temperature of 72°C for 35 s). Those cycles have been followed by a step of final extension at a temperature of 72°C for 5 min. Product length of rs1470579 A > C is 277 b digested with MseI endonuclease to 200 b and 77 b. Product length of rs4402960G > T (518 b) was digested by MboII to 380 b and 138 b. The products of the PCR confirmed by the electrophoresis on 2% agarose gels. The genotyping has been completed with the use of ultraviolet transilluminator. A minimum of 25% of samples have been regenotyped.

Statistical analyses

Analyses have been managed using the SPSS program V.25.0 (SPSS, Chicago, US). Continuous variables are organized as mean ± SD. Chi-square test had been employed for categorical variables that were organized as numbers and percentage values. Student's t-test was utilized for comparison of continuous variables to test between-group differences. Gene disease associations were calculated with the utilization of odds ratios (OR), 95% confidence interval (95% CI), and significance value that has been obtained by unconditional logistic regression analyses (ULR) that was adjusted for the BMI, age, and gender. Chi-square testing had been applied to test Hardy–Weinberg equilibrium (HWE) of genotype frequency values. Statistical significance was considered at two-tailed $p < 0.050$.

Results

In total, 400 T2DM as 174 males and 226 females (50.59 ± 9.16 years) and 400 controls as 222 males and 178 females (47.84 ± 7.61 years) have been included in the analysis. Considerably, patients exhibited higher values of the BMI, FPG, Tgs, TC, and LDL-C than the healthy control members (p < 0.0001) (Table 1).

Table 1: Biochemical parameters differences between the T2DM and control group

Parameters	Participants		p-value
	T2DM	Control	
	Mean ± SD	Mean ± SD	
Sex (M/F)	174/226	222/178	0.001
Age	50.59 ± 9.16	47.84 ± 7.61	<0.0001
BMI	25.9 ± 1.15	23.97 ± 2.44	<0.0001
VLDL (mg/dl)	31.73 ± 2.16	22.32 ± 4.58	<0.0001
FBG (mg/dl)	207.08 ± 26.2	77.84 ± 10.55	<0.0001
Tgs (mg/dl)	158.66 ± 10.8	111.6 ± 22.89	<0.0001
TC (mg/dl)	201.08 ± 28.8	159.24 ± 18.2	<0.0001
HDL (mg/dl)	42.61 ± 10.64	47.6 ± 9.76	<0.0001
Insulin (μU/ml)	7.99 ± 1.2	3.06 ± 1.18	<0.0001
LDL (mg/dl)	126.74 ± 30.92	89.32 ± 20.89	<0.0001
HOMA-IR	4.08 ± 0.77	0.59 ± 0.24	<0.0001

T2DM: Type 2 diabetes mellitus, BMI: Body mass index, FBG: Fasting blood glucose, VLDL: Very low-density lipoprotein, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Tgs: Triglyceride, TC: Total cholesterol, HOMA-IR: Homeostatic model assessment for insulin resistance, SD: Standard deviation.

Genotype analysis of the two SNPs of IGF2BP2 is explained in Table 2. The SNP rs4402960 showed that the minor allele frequency of T allele was significantly different between both groups of participants (p = 0.0013) with 33.6% in T2DM group. Homovariant TT shows a significant (p < 0.0001) odds ratio (4.5) as codominant type after adjusted to age, gender, and BMI. Similarly, dominant and recessive models exerted significant p = 0.02 and p < 0.0001, respectively) adjusted odds ratio (1.45 and 4.14, respectively). The rs1470579 SNP showed a significant p = 0.024 odds ratio (1.28) of C allele in the patients group than in A allele. The CC genotype in codominant and recessive models showed significant (0.03) odds ratio differences (2.03 and 1.96, respectively), as shown in Table 2.

The codominant model of rs4402960 shows significant p = 0.023 and p = 0.0002 differences of fasting insulin and BMI, the data not mention in tables. The other biochemical parameters mentioned no significant difference among genotype groups. However, the rs1470579 SNP analysis exerted significant differences as codominant model in features of BMI, FBG, insulin, and HOMA-IR, as mentioned in Table 3. The study power of rs4402960 is 69.5% and rs1470579 is 34.1%.

Discussion

The links between T2DM and IGF2BP2 polymorphisms were studied in numerous researches appropriately, but the association stayed uncertain. This study bears out the association of rs4402960 and rs1470579 polymorphism and T2DM among Iraqi people. The risk of T and C alleles is evidently significant as recessive in the two SNPs (p < 0.0001 and 0.03, respectively).

A meta-analysis produced an accurate estimation of effect size with substantially high statistical power that is mainly important in a case of a small sample size result in a limited power study [23]. Results of the meta-analysis have shown that rs-4402960 and rs-1470579 were highly related to T2DM susceptibility in Asian populations [24]. The study detected dominant and recessive effects of rs4402960 SNP, but the rs1470579 SNP only seemed to have a recessive effect. In general, associations between IGF2BP2 polymorphism and T2DM had been significantly found

Table 2: Genotype analysis of rs4402960 and rs1470579 SNPs

IGF2BP2 polymorphisms	Cases	Controls	Crude model OR (95% CI)	p-value	Adjusted model* OR (95% CI)	p-value
rs4402960	n = 400	n = 400				
Allele (%)						
G	531 (66.37)	590 (73.75)				
T	269 (33.63)	210 (26.25)	1.42 (1.15 ± 1.77)	0.0013		
Genotype (%)						
GG	177 (44.25)	217 (54.25)				
GT	177 (44.25)	156 (39)	1.39 (1.04 ± 1.86)	0.03	1.21 (0.86 ± 1.69)	0.28
TT	46 (11.5)	27 (6.75)	2.09 (1.25 ± 3.5)	0.01	4.51 (2.19 ± 9.25)	<0.0001
Dominant (%)						
GG	177 (44.25)	217 (54.25)				
TT+TG	223 (55.75)	183 (45.75)	1.49 (1.13 ± 1.97)	0.01	1.45 (1.05 ± 2)	0.02
Recessive (%)						
TG+GG	354 (88.5)	373 (93.25)				
TT	46 (11.5)	27 (6.75)	1.8 (1.09 ± 2.95)	0.02	4.14 (2.05 ± 8.38)	<0.0001
rs1470579	n = 400	n = 400				
Allele (%)						
A	546 (68.25)	587 (73.38)				
C	254 (31.75)	213 (26.62)	1.28 (1.03 ± 1.59)	0.024		
Genotype (%)						
AA	186 (46.5)	216 (54)				
AC	174 (43.5)	155 (38.75)	1.3 (0.97 ± 1.75)	0.08	1.09 (0.78 ± 1.52)	0.62
CC	40 (10)	29 (7.25)	1.6 (0.96 ± 2.69)	0.07	2.03 (1.08 ± 3.84)	0.03
Dominant (%)						
AA	186 (46.5)	216 (54)				
CC+AC	214 (53.5)	184 (46)	1.35 (1.02 ± 1.78)	0.034	1.20 (0.78 ± 1.66)	0.26
Recessive (%)						
AA+AC	360 (90)	371 (92.75)				
CC	40 (10)	29 (7.25)	1.42 (0.86 ± 2.34)	0.17	1.96 (1.05 ± 3.63)	0.03

*Adjusted for age, sex, and BMI. OR: Odds ratio, CI: Confidence interval.

Table 3: Biochemical parameters and anthropometric differences of rs1470579 SNP

Codominant rs1470579	Mean ± SD			p-value
	AA (186)	AC (174)	CC (40)	
Age (year)	49.37 ± 9.18	49.3 ± 8.65	51.4 ± 9.4	0.39
BMI	25.89 ± 1.17	26.07 ± 1.13	25.26 ± 0.82	0.0002
HDL-C (mg/dL)	43.05 ± 10.46	43.12 ± 10.03	44.06 ± 10.07	0.85
FBG (mg/dL)	209.03 ± 25.73	201.27 ± 27.64	205.57 ± 27.22	0.02
Tgs (mg/dL)	158.48 ± 11.65	157.56 ± 10.73	153.91 ± 8.61	0.06
TC (mg/dL)	204.15 ± 28.3	201.19 ± 30.02	201.12 ± 27.63	0.59
Insulin (μU/mL)	8.06 ± 1.17	8.01 ± 1.12	7.27 ± 1.25	0.0004
VLDL-C (mg/dL)	31.7 ± 2.33	31.51 ± 2.15	30.78 ± 1.72	0.06
LDL-C (mg/dL)	129.41 ± 30.99	126.56 ± 32.11	126.28 ± 33.22	0.66
HOMA-IR	4.17 ± 0.83	3.99 ± 0.81	3.7 ± 0.82	0.0027

BMI: Body mass index, FBG: Fasting blood glucose, VLDL: Very low-density lipoprotein, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Tgs: Triglyceride, TC: Total cholesterol, HOMA-IR: Homeostatic model assessment for insulin resistance, SD: Standard deviation.

under recessive genetic models. These results are affected by a small recessive genotype and inadequate statistical power in certain models. In addition, certain researches have shown that recessive IGF2BP2 polymorphisms associate with T2DM risk [25], [26], although others found this risk with dominant genetic models [27], [28].

Development complex diseases for instance T2DM involve a number of factors and polygenic. In general, it had been assumed that every one of the causing factors and genes participate in a small extent in the variability of phenotype. Furthermore, complex traits have common genetic heterogeneity and refer to the manifestation of genetic defect diversity that results in the same disease within clinical frames. Consequently, the genetic variability and etiology may partially explain the unpredictable associations between polymorphisms of IGF2BP2 (rs-4402960 and rs-1470579) and T2DM in diverse models and a variety of populations.

IGF2BP2 is a signaling molecule important for insulin action and growth and has an effect on the development of the pancreas in animal models [29]. Furthermore, the increased levels of FPG, TC, and postprandial serum insulin detected among T2DM that carried C allele of re1470579 SNP matched with AA carrier model [30]. The conditional inactivation of the IGF2BP2 in the pancreatic islets of mouse impaired insulin secretion by glucose induction [31]. Comparable results have been observed as well in several researches in diverse populations [32]. Therefore, it may be possible that IGF2BP2 variations have an important impact on functional regulation of pancreatic β-cell [30]. However, the assumption that the influence of T2DM predisposing types may be elicited affecting IGF2BP2 expression regulation that is related to the location of the SNPs (rs4402960 and re1470579) in intron 2 site within 50 kb [33]. Moreover, these variants could be related to proximate other variants that participate in microRNAs, greater no-coding transcripts, and other effects [30]. In addition, the SNPs rs4402960 and re1470579 are possibly substitution markers instead of real functional variants. The gene diacylglycerol kinase g-1 (DGKG) located in the region close to IGF2BP2 was reported to associate with the regulation of insulin secretion [34]. Therefore, additional functional studies are required for IGF2BP2 pathophysiological mechanisms.

Conclusion

The genetic susceptibility of IGF2BP2 has been detected to affect T2DM susceptibility under diverse genetic models. The study confirmed associations of rs-4402960 as codominant, dominant, and recessive with T2DM significantly. However, rs1470579 is associated as recessive model with T2DM in Iraqi population.

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