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Genetic Polymorphism and Risk of having Type 2 Diabetes in a Palestinian Population: A Study of 16 Gene Polymorphisms

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Keywords: Type-2 Diabetes; Gene; Single Nucleotide Polymorphism; Palestine

Abstract

Background: Type 2 Diabetes (T2D) is a multifactorial disease that encompasses environmental risk factors and the contribution of multiple genomic variants. Studies on the genetic components of T2D revealed many T2D-associated genetic polymorphisms in various populations. Lack of studies on the relation between gene polymorphism and T2D in Palestinians prompted us to examine the association between 16 known single nucleotide polymorphisms (SNPs) and T2D in this unexplored population.

Method: In this case-control study, 100 T2D male patients and 100 control men were examined. The two groups were genotyped for the 16 genes polymorphisms using PCR-Restriction Fragment Length Polymorphism (PCR-RFLP) technique. Body Mass Index (BMI), and essential clinical parameters were measured for all the study participants. The relation between the 16 SNPs and T2D were statistically analyzed using appropriate tests.

Results: Significant association was evident between IGF2BP and T2D, followed by CDKN2A/B (rs10811661) (OR=2.35, P-value=0.003), COL8A1 (rs792837) (OR=2.03, P-value=0.015), KCNQ1 (rs2237892) (OR=0.184, P-value=0.017), and KCNJ11 (rs5219; E23K) (OR=1.81, P-value=0.04), based on Armitage trend test. Among the 16 tested polymorphisms, a highly statistically significant association was evident between IGF2BP2 (rs4402960) and T2D [Odds ratio (OR)=3.28, P-value=7.46x10-8].

Conclusion: IGF2BP, CDKN2A/B, COL8A1, KCNQ1, and KCNJ11 gene variants are associated with T2D in the investigated population. This preliminary study sheds some light on the genetic components of T2D in Palestine.

Introduction

Type 2 Diabetes (T2D) is a global health concern with more than 300 million patients worldwide, and its prevalence is continuing to escalate in many populations [1], including Palestine. The estimated prevalence of diabetes in Palestinians, by the year 2010, was around 14% [2].

T2D is multifactorial disease that develops and progresses as a result of interaction between multiple genomic (both genetic and epigenetic) variants and various environmental factors [3,4].

Genetic alterations, in the form of single nucleotide polymorphisms (SNPs), in more than 80 loci have been associated with the susceptibility of having T2D in various populations, Caucasians in particular [5,6]. Functional studies have shown that many of those loci are related to the main aspects of T2D pathophysiology namely, insulin secretion and insulin resistance (and its underlying obesity) in peripheral tissues [7].

The gene polymorphisms investigated in the present study and their potential pathomechanisms in T2D were previously reported [8-12]. Earlier studies have shown that, at least for certain genetic polymorphisms, gender influences the outcome of association with T2D and that men and women genotypes should be assessed separately [13,14].

The Gaza strip is a small area (365 km^2) located in the south-western part of Palestine. It lies at the Mediterranean southeast coast. The strip is inhabited by around 2 million people.

Palestinians genetic susceptibility to T2D is largely unexplored, therefore this preliminary study was undertaken in order to identify some of the genetic risk alleles at reported SNPs.

Methods

Ethics approval and consent to participate

Written informed consent was obtained from all participants, and approval for conducting the study was obtained from the local Helsinki ethics committee.

Subjects

Two hundred males, including 100 unrelated T2D patients and 100 controls without diabetes, were enrolled in this study. T2D patients were recruited from Governmental Diabetes clinics in Gaza strip. BMI and relevant clinical parameters of the study participants are indicated in Table 1. All subjects were in the age range of 35 to 50 years.

DNA extraction

The DNA was isolated from whole blood samples using Wizard DNA extraction kit (Promega, USA) as described by the manufacturer.

SNP Selection and Genotyping

Sixteen SNPs validated for association with T2D in other populations have been investigated in this study (Table 2). SNPs were selected on basis of their consistent association with T2D reported in diverse populations [8-12].

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Table 1: Summary of the main characteristics of the study subjects.

Parameter	T2D Patients	Controls	P-value
BMI (kg/m^2 ±SD)	30.27±4.60	27.89±3.98	**<0.01**
C-peptide (ng/ml±SD)	1.80±0.86	1.95±0.75	0.2
Total Cholesterol (mg/dL±SD)	191.44±32.27	193.10±36.75	0.74
Triglycerides (mg/dL±SD)	181.39±95.54	148.50±100.98	**0.02**
HDL-C (mg/dL±SD)	49.55±3.04	49.68±3.39	0.78
LDL-C (mg/dL±SD)	109.80±32.24	115.45±34.10	0.23
HbA1c (%±SD)	8.46±1.73	5.40±0.31	**<0.01**

BMI: Body Mass Index; HbA1c: Haemoglobin A1c; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol.

Table 2: Summary of the gene SNPs tested in the current study.

SNP	Nearest Gene(s)	Chr. (Location)	Probable Role in T2D
rs1801282 C/G	PPARG	3p25.2 (Exonic)	Adipocyte differentiation
rs792837 G/C	COL8A1	3q12.1 (Intronic)	Pancreatic cell functioning
rs4402960 G/T	IGF2BP2	3q27.2 (Intronic)	Insulin pathway regulation
rs10010131 A/G	WFS1	4p16.1 (Intronic)	Beta-cell function/insulin response
rs4457053 A/G	ZBED3	5q13.3 (Intergenic)	Unknown
rs10946398 A/C	CDKAL1	6p22.3 (Intonic)	Beta-cell function/insulin secretion
rs972283 G/A	KLF14	7q32.2 (Intergenic)	Body mass index and insulin associated
rs13266634 C/T	SLC30A8	8q24.11 (Exonic)	Beta-cell function/insulin secretion
rs10811661 C/T	CDKN2A/B	9p21.3 (Intergenic)	Beta-cell formation
rs7034200 A/C	GLIS3	9p24.2 (Intronic)	B-cell function/regulation of insulin expression
rs1111785 G/A	HHEX/IDE	10q23.3 (Intergenic)	B-cell function/insulin secretion
rs793146 C/T	TCF7L2	10q25.2 (Intronic)	B-cell function/insulin secretion
rs5219 C/T	KCNJ11	11p15.1 (Exonic)	B-cell function/insulin secretion
rs2237892 C/T	KCNQ1	11p15.5 (Intronic)	B-cell function/insulin secretion
rs680 A/G	IGF2	11p15.5 (Exonic)	Pancreatic β-cell growth and development
rs8050136 A/C	FTO	16q12.2 (Intronic)	Body mass index-associated

PCR-RFLP was used for genotyping the selected SNPs. The PCR primers for genotyping COL8A1, WFS1, ZBED3, KLF14, and GLIS3 SNPs were designed using online Primer3 software (http://primer3.ut.ee/) based on the genomic sequence of each SNP (http://www.ncbi.nlm.nih.gov/snp/). Then restriction enzymes required for the PCR-RFLP identification of each SNP were selected from New England Biolabs (NEB) database by using NEBcutter V2.0 online software (http://nc2.neb.com/NEBcutter2/). Genotyping of the FTO polymorphism was carried out using allele-specific PCR. Primers, enzymes, and reaction conditions for the rest of the SNPs were as previously reported [15-23,32]. Sequences of the PCR primers employed in this work are presented in Table 3.

PCR was performed to amplify each required fragments. In a reaction mixture of 20 μL containing: 10 μL master mix (Promega, USA), 10 mmol/L of each primer, and 100ng genomic DNA. A typical 35 amplification cycles consisted of 30 seconds at 96 °C, 45 seconds at annealing temperature (Table 3), and 30 seconds at 72 °C. The final elongation step was 5 minutes at 72 °C. Restriction enzyme digestion was carried out as instructed by the manufacturer (NEB, Ipswich, MA, USA). The restricted PCR products were visualized by electrophoresis in 3% agarose gel stained with ethidium bromide. Alleles and genotypes were assigned according to the product sizes indicated in Table 3.

Statistical analysis

The genotype/allele frequencies in T2D patients and the controls were analyzed by standard Chi-square test. Logistic regression was used for computing "unadjusted" odds ratios and their corresponding 95% confidence intervals (CIs) considering diabetes as the dependent variable and the genotypes as independent variables. Student's t-test was used to evaluate the differences of the continuous variables (presented as mean ± standard deviation) between cases and controls. Hardy-Weinberg equilibrium (HWE) was tested using freely available software (http://www.oege.org/software/hwe-mr-calc.shtml). The Armitage trend test was applied to assess for the presence of association between the different groups of genotypes.

Results

Genotype and allele frequencies of investigated polymorphisms

Table 4 illustrates genotype/allele frequencies, odds ratios, 95% confidence intervals, crude P values and Armitage P trend values for the tested genes' polymorphisms among T2D patients and controls. Statistical analyses of genotypic and allelic frequencies for the tested SNPs revealed significant trend (all P trend values are <0.05) difference between T2D patients and controls in 5 of the tested genes (COL8A1, IGF2BP2, CDKNA2A/B, KCNJ11, and KCNQ1) polymorphisms. The remaining SNPs do not seem to impact T2D risk in the investigated population.

Apart from WFS1 (rs10010131), ZBED3 (rs4457053) and CDKNA2A/B (rs10811661) genotypes, which showed the corresponding P-values for those three SNPs were: <0.001, 0.008, and 0.008, all the other tested SNPs' genotypes were in Hardy-Weinberg equilibrium in the control group.

As presented in the Table 4, the strongest significant association (a common OR=3.28) was evident between IGF2BP2 variant and T2D where the minor (T) allele and the TT genotype have a clear impact on the risk of disease in the patient group in an additive manner. To a lesser extent, the CDKNA2A/B polymorphic (T) allele polymorphism has a moderate effect on T2D development. A lower, but significant effect was also observed for COL8A1, KCNJ11, and KCNQ1 polymorphisms.

In COL8A1, IGF2BP2, CDKNA2A/B and KCNJ11, the minor allele and its homozygous genotype (when available) presented the risk-associated allele. In KCNQ1, however, the polymorphic allele seems to be protective.

Discussion

Genetic variation, in terms of SNPs in more than 80 loci are reported as risk alleles for T2D in various populations [5,6,24]. Variations in

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Table 3: Primers and restriction enzymes used for genotyping of the investigated SNPs.

SNP	Enzyme	Primers 5'-3'	Annealing Temp. (°C)	Product size
PPARG rs1801282	HpaII	F: CAAGCCCAGTCCTTTCTGTG R: GCTATGACCAGTGAAGGAATCGCTTTCC	63	247 bp G: uncut C: 217+30 bp
COL8A1 rs792837	MmeI	F: CAGCCTGATCAGCATGAATCT R: CAGTCCTAATGAACAGCTTGTGA	57	704 bp T: uncut C: 472 bp+232 bp
IGF2BP2 rs4402960	MseI	F: CCCATCCTGAGGCAGTAAGA R: GGAGTTTGAGACCAGCCTTG	59	500 bp G: uncut T: 294 bp+206 bp
WFS1 rs10010131	BsmFI	F: GCATCCTTCCCTGGTAACCA R: GGGGTTGAGCTTCCAGTACA	58	247 bp A: uncut T: 132 bp+115 bp
ZBED3 rs4457053	AclI	F: TAATCAATGCCCTGGCTACC R: CCCACCAGAGGGGAAGTAAT	59	701 bp A: uncut G: 403 bp+298 bp
CDKAL1 rs10946398	AciI	F: CTGCTTGCTGTTGGGGAAGA R: CTCAATGCTGTTCATCAGGCAC	58	157 bp G: uncut C: 121+36 bp
KLF14 rs972283	SexAI	F: ATCAGTGCAGGGTCTCTAGC R: AGGGAGGGAGGAAGATCTGT	58	245 bp A: uncut G: 140 bp+105 bp
SLC30A8 rs13266634	HpaII	F: GAAGTTGGAGTCAGAGCAGTC R: TGGCCTGTCAAATTTGGGAA	60	256 bp T: uncut C: 176+80 bp
CDKN2A/B rs10811661	BspHI	F: CCGGCCCATTTTCTTTGTCA R: CAAAGCGCTGGGATCATAGG	61	232 bp C: uncut T: 164 bp+68 bp
GLIS3 rs7034200	AccI	F: ACGCCAACAGATTTCTCAAACA R: TGCCATTTCATTCACACTCTATG	56	198 bp C: uncut A: 118 bp+80 bp
HHEX/IDE rs1111785	XbaI	F: CATCATAACTTCTCACTCCCTTCC R: GCTGCTTATGGAAACTGCATTACT	60	161 bp G: uncut A: 111bp+50 bp
TCF7L2 rs793146	RsaI	F: ACAATTAGAGAGCTAAGCAC R: GTGAAGTGCCCAAGCTTCTC	59	188 bp T: uncut C: 159+29 bp
KCNJ11 rs5219	BanII	F: GACTCTGCAGTGAGGCCCTA R: ACGTTGCAGTTGCCTTTCTT	62	210 bp E: 150,32,28 bp K: 178,32 bp
KCNQ1 rs2237892	MspI	F: CTTGTGCCCTTGTCACCCAC R: GGCTTCCAGCCTCCAAGCTG	61	354 bp T: uncut C: 269+85 bp
IGF2 rs680	ApaI	F: CTTGGACTTTGAGTCAAATTGG R: CCTCCTTTGGTCTTACTGGG	55	236 bp A: uncut G: 175 bp+61 bp
FTO rs8050136	-	F-normal: TGCCCACTGTGGCAATA F-mutant: TGCCCACTGTGGCAATC R-common: AGACTTTCTAGCCCTGAGATTGT	57	246 bp

the genome- SNPs in particular-affect the level and function of gene expression and may modify the risk for having T2D. In this work, we could replicate the association between five documented SNPs and T2D in a Palestinian population. The significantly associated loci belong to one important aspect of T2D namely, pancreatic β-cell function/insulin secretion [7,25]. Additionally, the replication of those loci in Palestinian subjects further extends the trans-ethnic importance of many T2D genetic variants. The relatively small sample size employed presents one limitation of the current study and may reduce the chance of detecting the true effect of the investigated variants. Therefore, significant polymorphisms, in particular, need to be tested on a larger sample. On the other hand, selecting only middle age male subjects for the study makes the association between genetic variants and T2D more reliable.

Relevant to the pancreatic β-cell function/insulin secretion, our results showed that the genotype/allele frequencies of COL8A1 (rs792837 G>C), IGF2BP2 (rs4402960 G>T), CDKN2A/B (rs10811661 C>T), KCNJ11 (rs5219 C>T; E23K), and KCNQ1 (rs2237892 C>T) are significantly different between T2D patients and controls. Consistent with our results, significant association of these SNPs have been revealed also in other populations of diverse ancestries [26-32].

Despite their well-documented role in T2D in many genome-wide association studies and meta analyses [24,33], TCF7L2 (rs793146), CDKAL1 (rs10946398), and SLC30A8 (rs13266634) did not show the same trend in our population. Still, lack of association of those polymorphism with T2D has been reported in some other populations [5,10,34,35].

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Table 4: Genotype and allele frequencies and their effects on T2D risk for the 16 tested genes' polymorphisms.

SNP	Allele	T2D Patients	Controls	Odds Ratio (95% CI)	P-Value	Armitage trend test OR (P value)
PPARG rs1801282	CC	88 (88%)	89 (89%)	Reference	-	1.10 (0.82)
	CG	12 (12%)	11 (11%)	1.10 (0.46 to 2.63)	0.825	
	GG	0.0 (0.0%)	0.0 (0.0%)	1.01 (0.02 to 51.53)	0.996	
	C allele	188 (94%)	198 (94.5%)	0.91 (0.39 to 2.12)	0.83	
	G allele	12 (6%)	11 (5.5%)			
COL8A1 rs792837	GG	50 (50%)	67 (67%)	Reference	-	**2.03 (0.015)**
	GC	50 (50%)	33 (33%)	2.03 (1.15 to 3.60)	**0.015**	
	CC	0 (0%)	0 (0%)	1.34 (0.03 to 68.52)	0.885	
	G allele	150 (75%)	167 (83.5%)	1.69 (1.03 to 2.76)	**0.037**	
	C allele	50 (25%)	33 (16.5%)			
IGF2BP2 rs4402960	GG	10 (10%)	49 (49%)	Reference	**-**	**3.28 (7.46e-08)**
	GT	67 (67%)	40 (40%)	8.21 (3.74 to 17.99)	**1.48E-08**	
	TT	23 (23%)	11 (11%)	10.24 (3.81 to 27.56)	**1.63E-08**	
	G allele	87 (43.5%)	138 (69%)	2.90 (1.92 to 4.35)	**0.0001**	
	T allele	113 (56.5%)	62 (31%)			
WFS1 rs10010131	AA	20	22	Reference	-	1.12 (0.73)
	AG	80	78	1.13 (0.57 to 2.23)	0.73	
	GG	0	0	1.10 (0.02 to 57.89)	0.96	
	A allele	120	122	0.96 (0.64 to 1.43)	0.84	
	G allele	80	78			
ZBED3 rs4457053	AA	47 (47%)	58 (58%)	Reference	-	1.56 (0.12)
	AG	53 (53%)	42 (42%)	1.56 (0.89 to 2.72)	0.12	
	GG	0	0	1.23 (0.02 to 63.24)	0.917	
	A allele	147 (73.5%)	158 (79%)	1.36 (0.85 to 2.16)	0.19	
	G allele	53 (26.5%)	42 (21%)			
CDKAL1 rs10946398	AA	44 (44%)	47 (47%)	Reference	-	1.24 (0.26)
	AC	44 (44%)	48 (48%)	0.98 (0.55 to 1.75)	0.94	
	CC	12 (12%)	5 (5%)	2.56 (0.83 to 7.87)	0.1	
	A allele	132 (66%)	142 (71%)	0.79 (0.52 to 1.21)	0.28	
	C allele	68 (34%)	58 (29%)			
KLF14 rs972283	GG	46 (46%)	29 (29%)	Reference	**-**	0.74 (0.08)
	GA	38 (38%)	55 (55%)	0.44 (0.23 to 0.81)	**0.009**	
	AA	16 (16%)	16 (16%)	0.63 (0.27 to 1.45)	0.278	
	G allele	130 (65%)	113 (56.5%)	0.70 (0.45 to 1.05)	0.082	
	A allele	70 (35%)	87 (43.5%)			
SLC30A8 rs13266634	CC	55 (55%)	53 (53%)	Reference	-	1.05 (1.00)
	CT	38 (38%)	42 (42%)	0.87 (0.49 to 1.56)	0.56	
	TT	7 (7%)	5 (5%)	1.35 (0.40 to 4.52)	0.55	
	C allele	148 (74%)	148 (74%)	1.00 (0.64 to 1.57)	1	
	T allele	52 (26%)	52 (26%)			
CDKN2A/B rs10811661	CC	37 (37%)	58 (58%)	Reference	**-**	**2.35 (0.003)**
	TC	63 (63%)	42 (42%)	2.35 (1.33 to 4.15)	**0.003**	
	TT	0 (0%)	0 (0%)	1.56 (0.03 to 80.32)	0.83	
	C allele	137 (68.5%)	158 (79%)	1.73 (1.10 to 2.72)	**0.018**	
	T allele	63 (31.5%)	42 (21%)			
GLIS3 rs7034200	AA	30 (30%)	29 (29%)	Reference	-	0.82 (0.32)
	AC	52 (52%)	44 (44%)	1.14 (0.60 to 2.19)	0.69	
	CC	18 (18%)	27 (27%)	0.644 (0.29 to 1.41	0.27	
	A allele	112 (56%)	102 (51%)	1.22 (0.82 to 1.81)	0.31	
	C allele	88 (44%)	98 (49%)			
HHEX/IDE rs1111785	GG	48 (48%)	59 (59%	Reference	-	1.31 (0.17)
	AG	45 (45%)	35 (35%)	1.58 (0.88 to 2.83)	0.124	
	AA	7 (7%)	6 (6%)	1.43 (0.45 to 4.55)	0.54	
	G allele	141 (70.5%)	153 (76.5%)	0.73 (0.47 to 1.15)	0.17	
	A allele	59 (29.5%)	47 (23.5%)			

TCF7L2 rs793146	CC	23 (23%)	35 (35%)	Reference	-	1.46 (0.06)
	CT	52 (52%)	47 (47%)	1.68 (0.87 to 3.25)	0.48	
	TT	25 (25%)	18 (18%)	2.11 (0.97 to 4.72)	0.07	
	C allele	98 (49%)	117 (58.5%)	0.68 (0.46 to 1.01)	0.06	
	T allele	102 (51%)	83 (41.5%)			
KCNJ11 rs5219	GG	53 (53%)	62 (62%)	Reference	-	**1.81 (0.04)**
	GA	35 (35%)	35 (35%)	1.45 (0.82 to 2.54)	0.2	
	AA	12 (12%)	3(3%)	4.68 (1.25 to 17.47)	**0.01**	
	G allele	141 (49%)	159 (79.5%)	0.62 (0.39 to 0.97)	**0.04**	
	A allele	59 (29.5%)	41 (20.5%)			
KCNQ1 rs2237892	CC	98 (98%)	90 (90%)	Reference	**-**	**0.184 (0.017)**
	CT	2 (2%)	10 (10%)	0.18 (0.04 to 0.86)	**0.017**	
	TT	0 (0%)	0 (0%)	0.92 (0.02 to 46.79)	0.97	
	C allele	198 (99%)	190 (95%)	5.21 (1.13 to 24.09)	**0.035**	
	T allele	2 (1%)	10 (5%)			
IGF2 rs680	AA	17 (17%)	22 (22%)	Reference	-	1.11 (0.65)
	AG	63 (63%)	57 (57%)	1.43 (0.69 to 2.96)	0.33	
	GG	20 (20%)	21 (21%)	1.23 (0.51 to 2.97)	0.64	
	A allele	97 (48.5%)	101 (50.5%)	1.08 (0.73 to 1.60)	0.68	
	G allele	103 (51.5%)	99 (49.5%)			
FTO rs8050136	AA	26 (26%)	27 (27%)	Reference	-	1.29 (0.18)
	AC	39 (39%)	51 (51%)	0.79 (0.35 to 1.08)	0.51	
	CC	35 (35%)	22 (22%)	1.65 (1.02 to 3.57)	0.19	
	C allele	109 (54.5%)	95 (47.5%)	1.32 (0.89 to 1.96)	0.16	
	A allele	91 (45.5%)	105 (52.5%)			

Conflicting results are a common place in genetic association studies performed on different populations. Possible explanations for discrepant results include one or more of the following: differences in the ethnicity (genetic background), the sample size (i.e. statistical power), the characteristics of the study subjects (e.g. undefined chronic illnesses), presence of nucleotide polymorphism(s) somewhere else in the examined genes, epigenetic alterations, linkage disequilibrium to other sequence variants in the vicinity of the studied locus, and prevailing environmental conditions. It should be emphasized that frequency of T2D risk alleles and/or their effect size may be ethnicity-related and in turn influence the detection of their association with T2D in a given population. Overall, T2D susceptibility variants may be categorized as common and ethnicity-specific that needs to be identified for each population [5].

Conclusion

Results of the present study revealed that the five of investigated polymorphisms are significantly associated with T2D and could represent the first elements of "SNPs panel" for predicting T2D risk in the investigated population, particularly IGF2BP2. Future work should be directed towards testing those polymorphisms in T2D female patients, confirming the current findings with a larger sample, and examining additional SNPs that may help in characterizing additional genetic components of T2D.

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