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ORIGINAL RESEARCH

SLC30A8, *CDKAL1*, *TCF7L2*, *KCNQ1* and *IGF2BP2* are Associated with Type 2 Diabetes Mellitus in Iranian Patients

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Background: Type 2 diabetes mellitus (T2DM) is a serious public health issue with significantly increasing rates across the world. The genome-wide association studies (GWAS) have previously manifested involved genes that remarkably enhance the risk of T2DM. In this study, the association of common variants with T2DM risk has been identified among Iranian population from Tehran province of Iran.

Methods: Here, the association of refSNPs with T2DM risk was examined on peripheral blood samples of 268 individuals including control group and patients with T2DM using the tetra amplification refractory mutation system (ARMS) methods and direct genomic DNA sequencing.

Results: Our study demonstrated that *SLC30A8* rs13266634 (T/C), *CDKAL1* rs10946398 (A/C), *TCF7L2* rs7903146 (C/T), *KCNQ1* rs2237892 (T/C), and *IGF2BP2* rs1470579 (A/C) polymorphisms are significantly associated with type 2 diabetes, but no significant association was identified for FTO rs8050136 and MTNR1B rs10830963 polymorphisms.

Conclusion: The prediction of refSNPs is remarkably needed for pharmacogenetics and pharmacogenomic approaches, in which the information would be useful for clinicians to optimize therapeutic strategies and adverse drug reactions in patients with T2DM.

Keywords: type 2 diabetes mellitus, T2DM, Iranian populations, the tetra amplification refractory mutation system, ARMS, the genome-wide association studies, GWAS

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial and complex metabolic disorder, characterized by chronic hyperglycemia due to impairment in insulin secretion and sensitivity.[1] The frequency of T2DM is enhancing gradually due to environmental factors and interplay of different variation in multiple genes.[2] The World Human Organization (WHO) estimated that the total number of individuals with T2DM will reach to 366 million throughout the world by 2030.[3] The hallmark factors, influencing the prevalence of diabetes, include age, gender, ethnicity, lifestyle, and obesity,[4] in which the prevalence of T2DM in Iranian population is approximately 7.7%.[5] There are several important genetic factors in T2DM including high incidence of diabetes among monozygotic twins compare to dizygotic twins, familial history, ethnicity and migration studies.[6,7]

IGF2BP2 is extremely expressed in pancreatic islets and binds to IGF-2 (insulin-like growth factor 2) that plays remarkable roles in localization, stability and translation of RNA.[8–10] KCNQ1 (potassium voltage-gated channel KQT-like

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subfamily, member 1) gene is expressed in pancreatic islets[11,12] and plays a central role for repolarization of the cardiac action potential and transportation of water and salt in epithelial tissues.[13] Mutations in KCNQ1 gene are involved in deafness and long QT syndrome.[14] Blockade of the channel with KCNQ1 inhibitors 293B resulting in insulin secretion,[11] indicating that KCNQ1 channels may play functionally significant roles in regulation of insulin secretion. Previous studies demonstrated that TCF7L2 is an important regulator of insulin production and is also expressed in pancreatic islets.[15] TCF7L2 plays a key role in expression and subsequent conversion of proinsulin into mature insulin through various TCF7L2-target genes and downstream regulatory signaling pathways.[15] Additionally, TCF7L2 may also affect the insulin clearance and insulin sensitivity.[15,16]

The FTO rs8050136 polymorphism is associated with high risk of T2D.[17–23] The FTO is a 2-oxoglutarate (2-OG) Fe(II) dependent demethylase. Previous studies demonstrated a potential role of FTO in nucleic acid repair.[24] According to the previous studies, the exact molecular signaling pathways of FTO involved in human adiposity, cancer, metabolic disorders, obesity and T2D remain largely unknown.[18,25,26] The MTNR1B is a new susceptibility gene involved in the regulation of glucose homeostasis and T2DM, encoding the melatonin receptor MT2, which is expressed in different tissues including pancreatic islets.[27–30] The rs13266634 (C/T) in the SLC30A8 gene is associated with increasing risk of T2D, encoding zinc transporter 8, which is primarily expressed in pancreatic β-cells. Additionally, the major C-allele of rs13266634 is associated with a lower early insulin response to glucose and a high risk of T2D.[31,32] Due to the limited number of controlled trials, there is to date no overall strong evidence supporting the theory that zinc supplementation may lower the risk of T2D in humans.[33] Previous studies demonstrated an interaction between plasma zinc levels and rs13266634 on T2D risk.[34] Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like (CDKAL1) gene, located in 6p22.3, is associated with T2DM.[35] *CDKAL1* gene encodes tRNA decoration enzyme, namely methyl transfer enzyme which is involved in 2-methylthio-N6-threonylcarbamoyladenosine synthesis of the 37th base of tRNA Lys(UUU).[36,37]

Zinc is an essential element for insulin secretion and storage.[38–40] Pancreatic beta cells contain the highest level of Zinc compared to other cells in the human body.[41] The genome-wide association studies (GWAS) have extended the progress and distribution of different genetic components in type 2 diabetes.[9] Today, there are at least 20 loci that are associated with T2DM risk, in which the SLC30A8 (rs13266634), CDKN2A/2B (rs10811661), HHEX (rs1111875) and TCF7L2 (rs7903146) play important roles in the risk of T2DM in European Caucasians.[9,31,42,43] In this study, the association of different refSNPs with T2DM was investigated for the prediction of T2DM risk among the Iranian population.

Materials and Methods

Specimen Collection and Ethical Statement

In this study, 268 peripheral blood samples, including 106 healthy and unrelated donors and 162 patients with T2DM, were obtained from Tehran Taban Health Care and Diabetes Clinic (TTHCDC) and Aramesh Genetic and Pathobiology Lab from Tehran. The whole peripheral blood samples collected in tubes containing ethylenediamine tetraacetic acid (EDTA) in a final volume of 2 mL. The written informed consent for participating in the study and allowing the publishing of information for genetic analysis were obtained from individuals. Approval to conduct this study was granted by the medical ethics committee of Shahid Sadoughi University of Medical Sciences and Health Services (approval number: IR.SSU.MEDICINE.REC.1395.90) in accordance with the Declaration of Helsinki. The inclusion criteria were patients older than 40 years who had lived with type 2 diabetes for more than 10 years. The exclusion Criteria were: having chronic diseases such as heart failure, chronic kidney disease, chronic lung disease, diabetic foot or limb amputation, and moderate to severe retinopathy. The exclusion criteria in the control group were chronic disease or fasting blood sugar>100 mg/dl.

DNA Extraction Protocol

The DNA from whole peripheral blood samples was extracted using PrimePrep Genomic DNA extraction kit (GeNet Bio). The quantity and quality of extracted DNA was measured using Nanodrop, and then run on a 1% agarose gel electrophoresis.

Primer Design

The forward and reverse primers for identification of genes were designed using the online Primer 1 program, available from http://primer1.soton.ac.uk/public html/primer1.html, developed by Ye and colleagues in 2001. The

details of primers were checked using BLAST through https://www.ncbi.nlm.nih.gov/tools/primer-blast/.

The two special set primers were designed by using the primer1 program (http://primer1.soton.ac.uk/public_html/primer1.html) developed by Ye et al (2001). The specificity of primers and their melting temperatures were checked using BLAST (http://www.ncbi.nlm.nih). The details of the primers are summarized in Table 1.

Procedure of Tetra Primer ARMS-PCR

Essential keys for optimization of tetra ARMS are ration determination of outer and inner primers and annealing temperature. The unspecific bands were solved using gradient PCR system and optimization of outer and inner primer concentrations. The PCR reaction was performed in a final volume of 25 ul containing 1 µL Mg, 2.5 µL Buffer, 0.5 µL dNTP, 0.2 µL Taq polymerase, 1µL forward outer primer, 1 µL reverse outer primer, 2 µL forward inner primer, 2 reverse inner primer,1 µL DNA and 13.8 µL H2O. The DNA amplification was carried out using ARMS PCR for SNPs. The details of PCR reaction were as follows: 95°C for 5 min for cycle preparation, 30 cycles of denaturation at (95°C for 30 sec, annealing for 30 sec with different temperatures), polymerization at 72°C for 30 sec, and final extension at 72°C for 5 min with 1 cycle. The amplified fragment was confirmed and analyzed on 1.5% agarose gel (Figure 1).

Single Nucleotide Polymorphisms (SNP) Identification

In this study, the SNPs were sequenced and the results were then identified using the National Center for Biotechnology Information (NCBI) database, available at http://www.ncbi.nlm.nih.gov/SNP.

Table 1 Represents List of Forward and Reverse Primers (Inner and Outer) Applied for Detection of SNPs

SNP ID	Forward and Reverse Primer Sequences (Outer & Inner)		Primer Tm (C°)	Product Size(bp)	
1470579	FO	5′-ACA GAA ACA CAA TAA GAT CAT CAC AT-3’	57.43	FO-RO	391
	RO	5′-AAA TTT TTT ATG GAC ACT GAA GGT C-3’	56.51	FO-RI	205
	FI	5′-ATC ATT AGA TAA GAT CCA TAC GAG CTA-3’	57.37	FI-RO	233
	RI	5′-CTT TTC TTG ATA GGC AGG GTG-3’	56.59		
2237892	FO	5′-CTG TGG GTA CAC AGC TTC CCT-3’	61.72	FO-RO	467
	RO	5′-CCT GGG TCA TCA GAC TAG GGT AG-3’	61.01	FO-RI	267
	FI	5′-GTC ACA GGA CTT TGC CAA CC-3’	59.33	FI-RO	239
	RI	5′-TTT CTA GGC CCC TCA CCA CA-3’	60.47		
7903146	FO	5′-TTT TTC ACA TGT GAA GAC ATA CAC-3’	56.15	FO-RO	429
	RO	5′-TTT ATA GCG AAG AGA TGA AAT GTA G-3’	55.10	FO-RI	269
	FI	5′-ATT AGA GAG CTA AGC ACT TTT TAG AGA T-3’	58.59	FI-RO	212
	RI	5′-CTC ATA CGG CAA TTA AAT TAT AGA G-3’	54.04		
8050136	FO	5′-CCA TAC CAA CCA AGG TCC T-3’	56.29	FO-RO	388
	RO	5′-CAC ACC AAG ATG GTC ATG TC-3’	56.43	FO-RI	237
	FI	5′-GTT GCC CAC TGT GGC AGT A-3’	60.23	FI-RO	189
	RI	5′-AAC CAC AGG CTC AGA TAC TG-3’	56.93		
10830963	FO	5′-GGT TAA AGA GGC TGT CTG GGA GG-3’	62.51	FO-RO	421
	RO	5′-AGC CTT TGT TCA GAA CCA TGC TG-3’	61.87	FO-RI	254
	FI	5′-AGT GAT GCT AAG AAT TCA CAC CAT GTG-3’	61.97	FI-RO	216
	RI	5′-GGC AGT TAC TGG TTC TGG ATT GG-3’	61.43		
10946398	FO	5′-CAG GAT CTT GTG CTC CTC AC-3’	57.98	FO-RO	424
	RO	5′-CCA ACA GCA AGC AGT TGA TT-3’	57.19	FO-RI	255
	FI	5′-GGA AAA GGG TTT AGT ATC GCT C-3’	55.67	FI-RO	214
	RI	5′-GAT GAC TTG ATG CAA TGA CAG TAT-3’	57.38		
13266634	FO	5′-CTG CTG ATA GCA TTT GGG ACA GG-3’	61.55	FO-RO	826
	RO	5′-CCA ATT GAT TGA TGG ATC TCA GTG C-3’	60.51	FO-RI	520
	FI	5′-GCT TCT TTA TCA ACA GCA GCC AGC T-3’	64.04	FI-RO	350
	RI	5′-CGA ACC ACT TGG CTG TCC CG-3′	63.66		

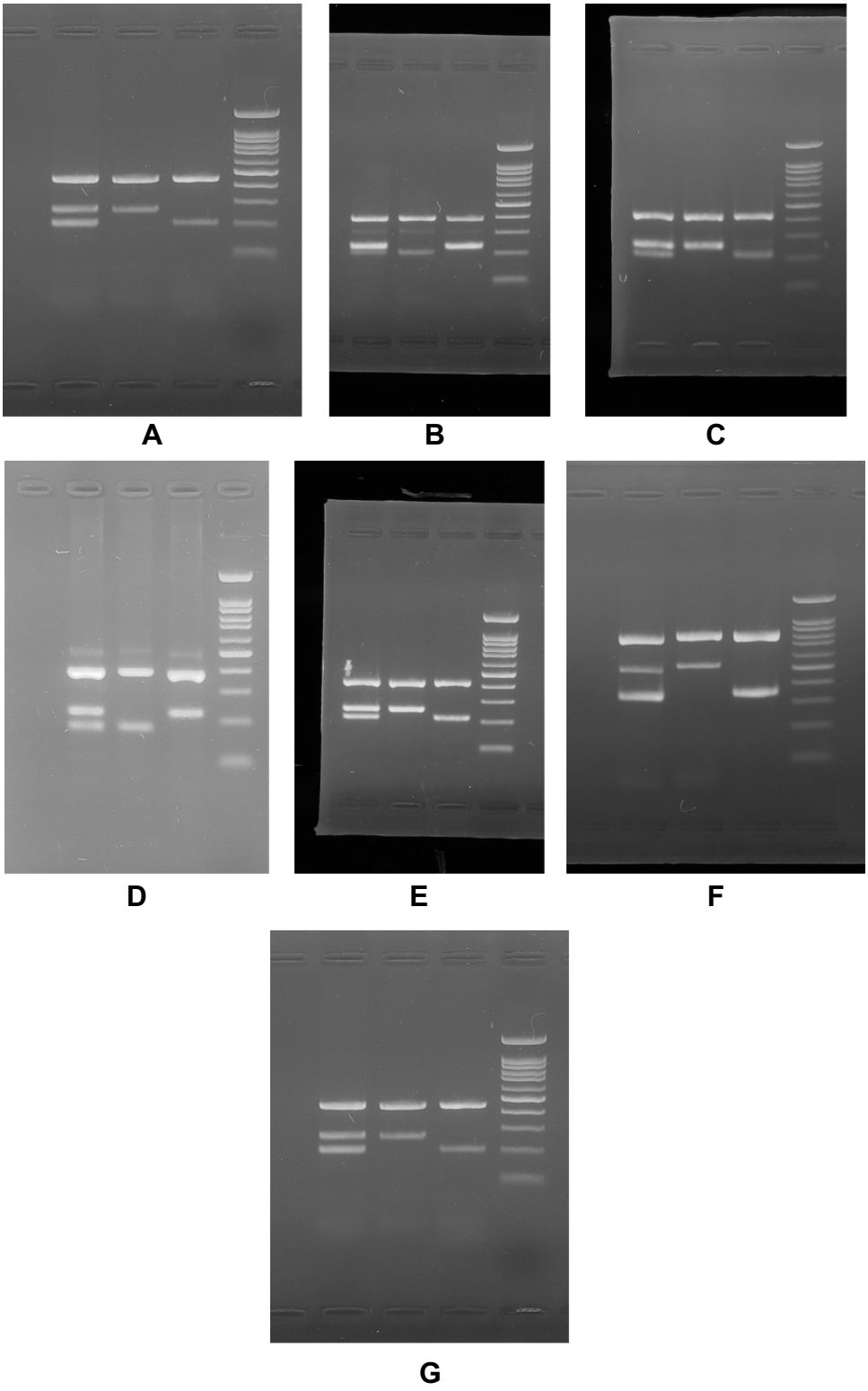

Figure 1 *ARMS-PCR* analysis of the (**A**) rs2237892 C > T, (**B**) rs1470579 C > A, (**C**) rs10946398 C > A, (**D**) rs8050136 A>C, (**E**) rs10830963 C > G, (**F**) rs13266634 C > T and (**G**) rs7903146 T > C on 1.5% agarose gel. Note: Lanes 1, 2, 3 and 4 represent fo-ro/fo-ri/fi-ro, fo-ro/fo-ri, fo-ro/fi-ro and DNA molecular marker, respectively.

Sequencing Analysis

The double-stranded DNA of PCR products was examined using an automated ABI sequencing machine (ABI 3130 Genetic Analyzer, Baghiyatallah Hospital, Tehran-Iran). The DNA fragments were confirmed for any nucleotide variation and were then analyzed using Finch TV software

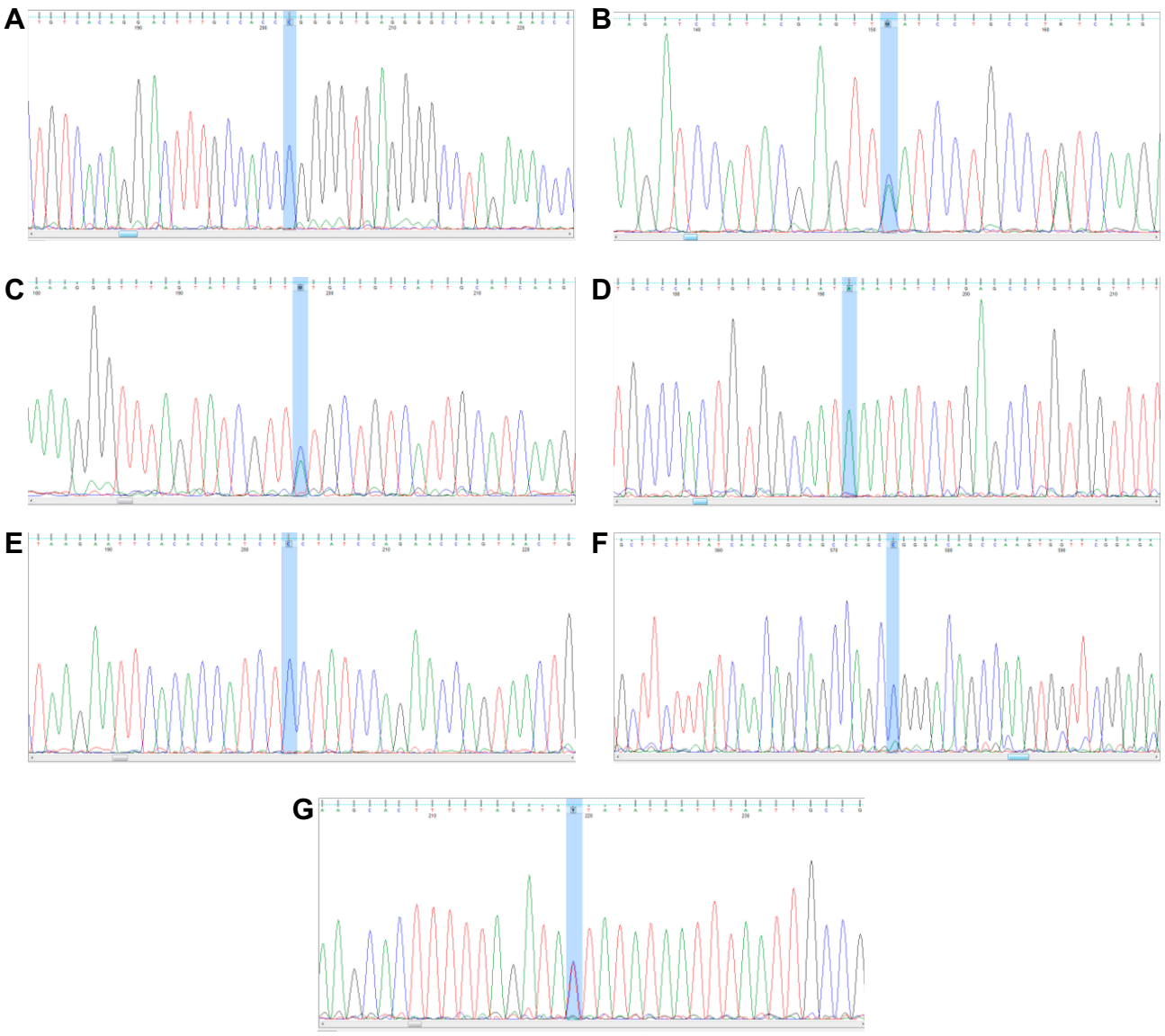

Figure 2 PCR-sequencing of (**A**) rs2237892 C > T, (**B**) rs1470579 C > A, (**C**) rs10946398 C > A, (**D**) rs8050136 A>C, (**E**) rs10830963 C > G, (**F**) rs13266634 C > T and (**G**) rs7903146 T > C. The highlighted blue area marks the polymorphisms.

(http://www.geospiza.com/finchtv/; PerkinElmer Inc., Waltham, MA, USA) (Figure 2).

Statistical Analysis

The odd ratios (OR) and 95% confidence intervals (CI) are used to determine the significant relationship of SNPs with T2DM. The Chi-square or Fisher exact test is used to analyze the results using STATA (V8) software. The *p*-values<0.05 is regarded as statistically significant.

Results

The clinical and biomedical characteristic of patients with T2DM were compared with control groups and the results are summarized in Table 2. This study demonstrated that there is a significant correlation (p<0.05) between T2DM patients and control groups with certain clinical parameters, including BMI, SBP, DBP, LDL, HDL, TG, 2hpp, FBS and HbA1c.

In our study, genotypic frequency of SNPs variants was analyzed from the blood samples of 162 T2DM patients and 106 non-diabetic individuals from the Iranian population. The genotypic frequencies of the homozygous (C/C), heterozygous (C/T), and homozygous (T/T) variants of the rs13266634 (T/C) significantly (P value<0.001) observed in 16 (9.88%), 64 (39.51%), and 82 (50.62%) of T2DM patients and 5 (4.72%), 23 (21.70%), and 78 (73.58. %) of

Table 2 The Clinical and Biomedical Characteristics of Individuals in This Study

Clinical Parameters	Controls (n=106)	T2DM Subjects (n=162)	P-value
Age	65.5±7.3	65±7.5	0.64
BMI (Body Mass Index)	23.07±1.03	24.00±1.23	<0.001*
SBP (Systolic Blood Pressure)	120.36±4.23	130.03±7.43	<0.001*
DBP (Diastolic Blood Pressure)	84.89±3.01	88.75±4.59	<0.001*
LDL (Low-Density Lipoprotein)	110.97±13.00	129.83±9.06	<0.001*
HDL (High-Density Lipoprotein)	46.07±4.16	44.28±4.29	0.002*
TG (Triglyceride)	118.64±12.11	176.69±11.59	<0.001*
2hpp (Two-Hour Postprandial Glucose)	121.56±3.60	235.35±12.97	<0.001*
FBS (Fasting Blood Sugar)	87.32±4.35	165.20±22.51	<0.001*
HbA1c (Glycated hemoglobin)	5.40±0.16	8.34±0.49	<0.001*

Notes: Data are mean±S.D values; *Statistically significant.
Abbreviations: BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; LDL, Low-Density Lipoprotein; TG, Triglyceride; 2hpp, Two-Hour Postprandial Glucose; FBS, Fasting Blood Sugar; HbA1c, Hemoglobin A1c.

the control groups, respectively (Table 3). Additionally, the odd ratio of T2DM patients with C/T and C/C genotype was 2.64 and 3.04, respectively. However, patients with C/T (P=0.001) and C/C (P=0.038) genotypes significantly indicated high risk of T2DM in comparison with T/T genotype. The genotypic frequencies of homozygous (A/A), heterozygous (A/C), and homozygous (C/C) variants of the rs10946398 (A/C) significantly (P value<0.001) observed in 31 (19.14%), 104 (64.20%), and 27 (16.67%) of T2DM patients and 46 (43.40%), 50 (47.17%), and 10 (9.43%) of the control groups. Additionally, the odd ratio of T2DM patients with A/C and C/C genotypes were 3.08 and

Table 3 The Genotypic Frequency of Polymorphisms Between T2DM and Control Groups

SNP		Control n (%)	T2DM n (%)	p-value
rs1470579 IGF2BP2	AA CC AC	55 (51.89%) 11 (10.38%) 40 (37.74%)	67 (41.36%) 55 (33.95%) 40 (24.69%)	0.001*
rs2237892 KCNQ1	TT CC CT	6 (5.66%) 85 (80.19%) 15 (14.15%)	1 (0.62%) 152 (93.83%) 9 (5.56%)	0.002*
rs7903146 TCF7L2	CC CT TT	51 (48.11%) 39 (36.79%) 16 (15.09%)	26 (16.05%) 76 (46.91%) 60 (37.04%)	0.001*
rs8050136 FTO	CC AA AC	25 (23.58%) 60 (56.60%) 21 (19.81%)	42 (25.93%) 73 (45.06%) 47 (29.01%)	0.132
rs10830963 MTNR1B	CC CG GG	52 (49.06%) 44 (41.51%) 10 (9.43%)	58 (35.80%) 80 (49.38%) 24 (14.81%)	0.079
rs10946398 CDKAL1	AA CC AC	46 (43.40%) 10 (9.43%) 50 (47.17%)	31 (19.14%) 27 (16.67%) 104 (64.20%)	0.001*
rs13266634SLC30A8	TT CC CT	78 (73.58%) 5 (4.72%) 23 (21.70%)	82 (50.62%) 16 (9.88%) 64 (39.51%)	0.001*

Note: *statistically significant.

Table 4 The Genotypic Frequency of Polymorphisms Between T2DM and Control Groups with Odds Ratio

SNP		Control n (%)	T2DM n (%)	Odds Ratio[a] (95% CI)	p-value
rs1470579 IGF2BP2	AA	55 (51.89%)	67 (41.36%)	Ref.	-
	CC	11 (10.38%)	55 (33.95%)	4.1 (1.96–8.59)	0.001*
	AC	40 (37.74%)	40 (24.69%)	0.82 (0.46–1.44)	0.494
rs2237892 KCNQ1	TT	6 (5.66%)	1 (0.62%)	Ref.	-
	CC	85 (80.19%)	152 (93.83%)	10.79 (1.27–90.6)	0.029*
	CT	15 (14.15%)	9 (5.56%)	3.6 (0.37–34.93)	0.269
rs7903146 TCF7L2	CC	51 (48.11%)	26 (16.05%)	Ref.	-
	CT	39 (36.79%)	76 (46.91%)	3.82 (2.07–7.03)	0.001*
	TT	16 (15.09%)	60 (37.04%)	7.35 (3.55–15.2)	0.001*
rs8050136 FTO	CC	25 (23.58%)	42 (25.93%)	Ref.	-
	AA	60 (56.60%)	73 (45.06%)	0.72 (0.39–1.32)	0.293
	AC	21 (19.81%)	47 (29.01%)	1.33 (0.65–2.72)	0.431
rs10830963 MTNR1B	CC	52 (49.06%)	58 (35.80%)	Ref.	-
	CG	44 (41.51%)	80 (49.38%)	1.63 (0.96–2.75)	0.068
	GG	10 (9.43%)	24 (14.81%)	2.15 (0.94–4.92)	0.069
rs10946398 CDKAL1	AA	46 (43.40%)	31 (19.14%)	Ref.	-
	CC	10 (9.43%)	27 (16.67%)	4.0 (1.70–9.43)	0.001*
	AC	50 (47.17%)	104 (64.20%)	3.08 (1.75–5.43)	0.001*
rs13266634 SLC30A8	TT	78 (73.58%)	82 (50.62%)	Ref.	-
	CC	5 (4.72%)	16 (9.88%)	3.04 (1.06–8.70)	0.038*
	CT	23 (21.70%)	64 (39.51%)	2.64 (1.49–4.67)	0.001*

Notes: [a]Crude odds ratio (95% CI); *statistically significant.

4.0, respectively. However, patients with C/C and A/C genotypes significantly (P=0.001) indicated high risk of T2DM in comparison with A/A genotype (Tables 3 and 4).

The genotypic frequencies of homozygous (C/C), heterozygous (C/T), and homozygous (T/T) variants of the rs7903146 (C/T) significantly (P value<0.001) observed in 26 (16.05%), 76 (46.91%), and 60 (37.04%) of T2DM patients and 51 (48.11%), 39 (36.79%), and 16 (15.09%) of control groups. Additionally, the odd ratio of T2DM patients with T/T and C/T genotype were 7.35 and 3.82, respectively. However, patients with T/T and C/T genotypes (P=0.001) indicated high risk in comparison with C/C genotypes (Tables 3 and 4).

The genotypic frequencies of homozygous (A/A), heterozygous (A/C), and homozygous (C/C) variants of the rs1470579 (A/C) significantly (P value<0.001) observed in 67 (41.36%), 40 (24.69%), and 55 (33.95%) of T2DM patients and 55 (51.89%), 40 (37.74%), and 11 (10.38%) of the control groups. Additionally, the A/C genotype was evaluated using odd ratio (OR: 4.1) and it was significantly high (P=0.001) in T2DM patients in comparison with A/A genotype (Tables 3 and 4). The genotypic frequencies of homozygous (T/T), heterozygous (C/T), and homozygous (C/C) variants of the rs2237892 (C/T) significantly (P value=0.002) observed in 1 (0.62%), 9 (5.56%), and 152 (93.83%) of T2DM patients and 6 (5.66%), 15 (14.15%), and 85 (80.19%) of the control groups. Additionally, C/C genotype was evaluated using odd ratio (OR: 10.7) and it was significantly high (P=0.029) in T2DM patients in comparison with the T/T genotype (Tables 3 and 4). Additionally, there is no significant association of rs8050136 FTO (p value = 0.132) and rs10830963 MTNR1B (p value = 0.079) polymorphisms between T2DM patients and control groups (Tables 3 and 4).

Discussion

Type 2 diabetes mellitus (T2DM) is a complicated multigene or polygenic disorder involved with unknown contributing genes that increase the risk of T2DM in susceptible individuals. Recently, 16 novel susceptible gene loci for T2DM were identified,[44] but the impact of TCF7L2 is much higher in comparison with other confirmed T2D gene candidate.[45]

The interaction of multiple genes and genetic and environmental factors lead to hyperglycemia due to impaired insulin function or secretion. Therefore, different strategies have been attempted to identify involved genes with T2DM. However, investigation in different ethnicities and geographical region demonstrated different results across the world. SNPs in SLC30A8 (rs13266634), *CDKAL1* rs10946398, TCF7L2 rs7903146, KCNQ1 rs2237892, IGF2BP2 rs1470579 and MTNR1B rs10830963 were reported to be associated with T2DM in different studies.[46–49] Our study demonstrated that *SLC30A8* rs13266634 (T/C), *CDKAL1* rs10946398 (A/C), TCF7L2 rs7903146 (C/T),KCNQ1 rs2237892 (T/C), and IGF2BP2 rs1470579 (A/C) polymorphisms are significantly in association with type 2 diabetes, but no significant association was identified for FTO rs8050136 and MTNR1B rs10830963 polymorphisms in present study.

Of 31 provinces in Iran, studies on only two provinces, Gorgan[50] and Kurdish,[51] revealed that the frequency of the TCF7L2 rs7903146 polymorphism was significant, which is in agreement with present study. In contrast to our study, a lack of remarkable association between TCF7L2 rs7903146 polymorphism and T2D was reported among the Arabian Emirates[52] and Saudi Arab population.[53] Here, the association of various SNPs with T2DM risk was investigated among Iranian individuals. However, the limitation of our study was to demonstrate the association of mortality and clinical complications with T2DM. The fundamental mechanisms, by which genetic variations within the intron of the TCF7L2 gene confers susceptibility to T2DM, remain to be elucidated. However, a study indicated that genetic variations around 3′end of the TCF&L2 gene may affect the function of TCF7L2, due to regulation of alternative splicing.[54] The lack of statistically significant differences in the allelic and genotypic frequencies of FTO rs8050136 and MTNR1B rs10830963 polymorphisms between T2DM and control groups may be partially interpreted due to the heterogeneity of the individual's ethnicity. It is accepted that approximately 14% of the between-studies variances may be attributed to ethnicity differences.[55]

Conclusion

In conclusion, our study indicated the association of well-established common variants of *SLC30A8* rs13266634 (T/C), *CDKAL1* rs10946398 (A/C), TCF7L2 rs7903146 (C/T), KCNQ1 rs2237892 (T/C), and IGF2BP2 rs1470579 (A/C) with type 2 diabetes among Iranian population from Tehran. Our study indicated the remarkable presence of the rs13266634, 10946398, 7903146, 2237892 and 1470579 polymorphisms in Iranian population, suggesting susceptibility of individuals to T2DM which may lead to identification of individuals with high risk for developing T2DM. Additionally, this study demonstrated the absence of the common variant FTO rs8050136 (C/A) among Iranian population. It is clinically important to manifest individuals for pharmacogenetics and pharmacogenomics approaches and prevention of harmful complication of this silent disease and adverse drug reactions. Therefore, identification of involved polymorphism analysis improves individual lifestyle and is a helpful tool toward personalized medicine and avoidance of the harmful effects of drugs.

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Author Contributions

Conceived the experiments: Seyed Mehdi Kalantar, Massoud Houshmand and Kazem Vatankhah Yazdi; Designed the experiments: Masoud Reza Manaviat and Masoud Rahmanian; Collection of specimens and consent form: Kazem Vatankhah Yazdi, Mohammad Reza Jahani; Performed the experiments: Kazem Vatankhah Yazdi; Analyzed the data: Amir Almasi-Hashiani; Contributed reagents/materials/analysis tools: Kazem Vatankhah Yazdi, Seyed Mehdi Kalantar and Massoud Houshmand; Wrote the paper: Kazem Vatankhah Yazdi and Behnam Kamalidehghan; Revised and approved the manuscript: Kazem Vatankhah Yazdi and Behnam Kamalidehghan. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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