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أنماط جينات *PPARG* و *IRS1* و *TCF7L2* و *KCNJ11* لدى الأفراد البدينين المصابين بالسكري وغير المصابين بالسكري

م.د. زينب ضياء جبوري الخطيب
قسم علوم الحياة / كلية العلوم / جامعة واسط
zalkhateeb@uowasit.edu.iq

المستخلص:

البدانة حالة معقدة متعددة العوامل تتأثر بعوامل بيئية وجينية، مما يؤدي إلى مضاعفات متنوعة مثل داء السكري من النوع الثاني. ومع ذلك، فإن التباينات الظاهرية تزيد من الاهتمام بدور التعددات الجينية في تعديل قابلية الإصابة بداء السكري من النوع الثاني لدى الأفراد المصابين بالبدانة . هدفت الدراسة الحالية الى تقصي التعبير الجيني والمخاطر المرتبطة بجينات *IRS1* و*KCNJ11* و*PPARG* و*TCF7L2* على المستوى الجزيئي لدى الأفراد البدينين ، سواءً كانوا مصابين بداء السكري من النوع الثاني (OT2DM) أو غير مصابين به (OND) . اجماليا ، تم اختيار ٩٠ شخصا بدينا، ٤٥ مصابا بداء السكري من النوع الثاني و٤٥ غير مصابين به ، حيث تم خضوعهم الى سحب عينات الدم الوريدي لغرض فحصه باستعمال الاختبارات الجزيئية والمصلية. استُخدم التنميط الجيني الجزيئي بتقنية تفاعل البوليميراز المتسلسل النوعي للأليلات مع تحليل تعدد أطوال قطع التقييد (PCR–RFLP) لتحديد النمط الجيني rs1801278 لجين *IRS1*، بينما استُخدمت تقنية تفاعل البوليميراز المتسلسل T–ARMS لتحديد النمط الجيني rs5219 لجين *KCNJ11*، وrs1801282 لجين *PPARG*، وrs7903146 لجين *TCF7L2*. أظهرت النتائج أن التباين الجيني (rs1801278) *IRS1* G>A مرتبطٌ ارتباطًا وثيقًا بداء السكري من النوع الثاني لدى الأفراد البدينين، كما وُجد أن النمطين الجينيين GA وAA هما الأكثر شيوعًا لدى الأفراد البدينين المصابين بالسكري من النوع الثاني مقارنةً بالأفراد غير المصابين به . بالإضافة إلى ذلك،

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لوحظ ارتفاعٌ ملحوظٌ في تكرار ونسبة الخطر في الأليل A لدى الأفراد المصابين بالسكري من النوع الثاني مقارنةً بالأليل G. مايخص جين *KCNJ11* C>T (rs5219)، كان تكرار النمط الجيني CT ومخاطره أعلى بكثير من النمطين CC وTT لدى الأفراد المصابين بداء السكري من النوع الثاني ، وكذلك مقارنةً بالأنماط الجينية لدى الأفراد غير المصابين به . وبصورة مماثلة ، كان تردد الأليل T ومخاطره أعلى من تردد الأليل C ومخاطره لدى الأفراد المصابين بداء السكري من النوع الثاني . أما بالنسبة لجين *PPARG* G>C (rs1801282)، فقد كانت نسبة النمطين الجينيين GC وCC ومخاطرهما أعلى بكثير من النمط الجيني GG لدى الأفراد المصابين بداء السكري ، وكذلك مقارنةً بالنمط الجيني GC لدى الأفراد غير المصابين بداء السكري. وأظهرت نتائج تردد الأليلات ارتفاعًا ملحوظًا في وجود الأليل C ومخاطره مقارنةً بالأليل G لدى الأفراد المصابين بداء السكري من النوع الثاني، وكذلك مقارنةً بالأليلين G وC لدى الأفراد غير المصابين بداء السكري من النوع الثاني. أظهرت نتائج تحليل الطفرة الجينية *TCF7L2* C>T (−rs7903146) أن تردد النمطين الجينيين CT وTT ومخاطرهما في الافارد البدينين والمصابين بالسكري من النوع الثاني كان أعلى بكثير مما هو عليه في الافراد البدينين غير المصابين بالسكري ؛ بينما كانت نسبة الأليل T ومخاطره في مرضى السكري من النوع الثاني أعلى بشكل ملحوظ من الأليل C. من هنا ، استنتجت هذه الدراسة إلى انتشار الطفرات الجينية *IRS1* G>A (rs1801278)، و *KCNJ11* C>T (rs5219)، و *PPARG* G>C (rs1801282)، و*TCF7L2* C>T (−rs7903146) وارتفاع خطرها لدى مرضى السكري من النوع الثاني المصابين بالبدانة مما يستدعي إجراء المزيد من الدراسات للتحقق من أدوار الجينات المختلفة وإمكانية استخدامها في تشخيص مثل هذه الاضطرابات الأيضية.

الكلمات المفتاحية: rs1801278، rs5219، rs1801282، وrs7903146، السكري من النوع الثاني، العراق.

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Patterns of *PPARG*, *IRS1*, *TCF7L2*, and *KCNJ11* Genes in Obese Diabetic and Non-Diabetic Individuals

Lecturer DoctorZainab Dhiyaa Jabuori Alkhateeb

Department of Biology / College of Science / University of Wasit

zalkhateeb@uowasit.edu.iq

Abstract:

Obesity is a complex multifactorial condition influenced by both environmental and genetic factors, resulting in various complications such as type2 diabetes mellitus (T2DM). However, phenotypic variations lead to increasing the interest about the role of genetic polymorphisms in modulating susceptibility to T2DM among obese individuals. This study aims to molecular identification the expression and risks of *IRS1*, *KCNJ11*, *PPARG* and *TCF7L2* genes among the obese individuals who having the T2DM (OT2DM) and non-diabetic (OND) with investigation the levels of lipid profiles and relationship to some demographic risk data. **Materials and methods:** Totally, 90 individuals (45 OT2DM and 45 were selected and subjected to collection of venous blood that examined molecularly and serologically. Molecular genotyping using allele-specific PCR-RFLP was served for SNPs targeting rs1801278 for *IRS1* while T-ARMS PCR was utilized for SNPs targeting rs5219 for *KCNJ11*, rs1801282 for *PPARG*, and rs7903146 for *TCF7L2* genes. The findings *IRS1 G>A* (rs1801278) were revealed a marked elevation in frequency and risk of GA and AA genotypes of OT2DM individuals when compared to OND population. In OT2DM, there was a significant higher frequency and risk of A allele than G allele. Regarding *KCNJ11 C>T* (rs5219), the frequency and risk of CT genotype was apparently higher than the CC and TT in OT2DM than OND. Subsequently, the OT2DM was reported a higher frequency and risk of T

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allele than C allele. Concerning *PPARG G>C* (rs1801282), values of frequency and risk of GC and CC genotypes were elevated more than the GG genotype among the OT2DM population; whereas, results of allele frequency in OT2DP were detected a marked elevation in existence and risk of C allele in comparison to G allele. Relation *TCF7L2 C>T* (-rs7903146), our findings identified that the frequency and risk of CT and TT genotypes in OT2DM population was significantly higher than OND. Subsequently, the percentage and risks of T allele in OT2MD population was markedly higher the C allele. In conclusion, this study indicates the predominant and risk of *IRS1 G>A* (rs1801278), *KCNJ11 C>T* (rs5219), *PPARG G>C* (rs1801282), and *TCF7L2 C>T* (-rs7903146) in OT2DM compared to OND suggesting importance of furthermore studies to investigate the roles of various genes in OT2DM, and possible utilization of such genes in determination of such metabolic disorders.

Keywords: rs1801278, rs5219, rs1801282, and rs7903146, Gene polymorphism, Iraq

Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterised by persistent hyperglycaemia due to impaired insulin production or insulin resistance or both (Al-Shaeli et al., 2022). T2DM is an increasingly critical health challenge in the world today and, with the shift in lifestyle, urbanization and increasing obesity prevalence, along with genetic susceptibility, is playing an increasingly important role in determining individual susceptibility (Chandrasekaran and Weiskirchen, 2024; Rob et al., 2025). The last decades, the importance of specific molecular genetic variations that are associated with glucose homeostasis, insulin signaling and pancreatic β-cell function was highlighted (Sami et al., 2025). There are several genes have been extensively studied with strong association to T2DM risk such as *insulin receptor substrate 1* (*IRS1*), *potassium inwardly rectifying channel subfamily J member 11* (*KCNJ11*), *peroxisome*

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proliferator-activated receptor gamma (*PPARG*), and *transcription factor 7-like 2* (*TCF7L2*), (Blanken et al., 2025; Rana et al., 2026).

The *IRS1* is a key cytoplasmic adapter protein that located on the chromosome 2q36 and widely expressed in insulin-sensitive tissues such as skeletal muscle, adipose tissue and liver (Szablewski, 2024). Upon insulin binding to its receptor, the receptor undergoes auto-phosphorylation and subsequently phosphorylates *IRS1* on specific tyrosine residues to create docking cites for various signaling molecules and influencing the glycogen synthesis, lipid metabolism and protein synthesis (Haider, 2023; Kumar, 2024).

KCNJ11 gene, which encodes the Kir6.2 protein, forms an essential part of the ATP-sensitive potassium (KATP) channel that is fundamental to the linking of the cellular metabolism to insulin secretion in pancreatic β-cells (Yang and Yang, 2025). The KATP channels are left open in low glucose conditions and the potassium ions move out of β-cells through maintaining the cell in a hyperpolarized state, and inhibition of insulin release (Merrins and Kibbey, 2024). During high blood glucose, the enhanced intracellular production of ATP closes the KATP channels and subsequent depolarization of the membrane, which causes an opening of voltage-dependent calcium channels, and stimulates the secretion of insulin (Oluwamodupe and Babalola, 2024).

As a key point of control in adipogenesis and lipid metabolism, the *PPARG* is a ligand-activated transcription factor, a nuclear hormone receptor (Yang et al., 2024). *PPARG* gene is among the significant genes that involved in pathogenesis of obesity and T2DM. This gene, located on chromosome 3p25, is largely expressed in adipose tissue with other genes, to regulate and express the adipocyte differentiation and fat storage (Veerabathiran et al., 2023; Dracheva et al., 2024). Moreover, *PPARG* gene plays an important role in insulin sensitivity, which is reflected in a reduced lipo-toxicity in insulin-sensitive tissues like liver and skeletal muscle, thereby enhancing insulin action, while promoting the storage of free fatty acids in adipocytes. This re-distribution of lipids enhances the uptake and use of glucose,

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glycemic control, and reducing the risk of insulin resistance (Giannopoulos et al., 2023; Jo, 2024; Singh et al., 2026).

TCF7L2 is a regulatory gene on chromosome 10q25.2-q25.3 that encodes a transcription factor, which is a central component of the Wnt/β-catenin signaling pathways involved in metabolic homeostasis as well as regulation of cell proliferation, differentiation and gene expression (Adeerjiang et al., 2025; Pati et al., 2025; Salamah et al., 2026). The functions of *TCF7L2* are done by binding to β-catenin and regulating the transcription of target genes involved in glucose production and insulin secretion; while in pancreatic β-cell and liver, it influences the biosynthesis and secretion of insulin and gluconeogenesis, respectively (Tian et al., 2024; Younus and Al-Faisal, 2024).

In Iraq, several studies have been conducted in last 10 years to investigate the role of *IRS1*, *KCNJ11*, *PPARG*, and *TCF7L2* genes solely among various diseased patients (Baqer and Shwan, 2023; Younus and Al-Faisal, 2024; Nasr et al., 2024; Mudhaffer and Hassan, 2025). Hence, this research aims to Molecular exploring the expression and risks of *IRS1*, *KCNJ11*, *PPARG* and *TCF7L2* genes among the T2DM and non-diabetic obese individuals.

Materials and methods

Samples and data

The present study was compromised an overall 90 obese individuals [45 T2DM (OT2DM) and 45 non-diabetes (OND)] who attended to a number of private clinician specialist in Al-Kut city during January (2026). Under aseptic conditions, 5ml of venous blood was drained from each individual, and divided equally into free-anticoagulant glass gel tube for serum obtaining as well as into an anticoagulant plastic tube (whole blood) for molecular testing. After centrifugation, the serum and whole blood samples were kept frozen (-20C) until be tested. Additionally, information concerning the age and sex of study population was reported as a risk factor.

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Molecular genotyping

After preparation at room temperature, the gSYNC™ DNA Extraction Kit (Genaid, Taiwan) was served to extract DNAs from the whole blood samples under restricted conditions. For preparation of Mastermix tubes, all samples of DNAs were genotyped using allele-specific PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) was served for SNPs targeting rs1801278 for *IRS1* gene while T-ARMS PCR (Tetra-primer Amplification Refractory Mutation System) was utilized for SNPs targeting rs5219 for *KCNJ11*, rs1801282 for *PPARG*, and rs7903146 for *TCF7L2* genes (Table 1), and Promega GoTaq™ G2 Green Master Mix Kit [Promega, Korea (Cat. No.PRM7822)]. The PCR mixtures prepared at a final volume of 20µL, were amplified in the Thermal Cycler under a modified condition (Table 2). The PCR-RFLP products were digested overnight with restriction enzyme (PstIrestriction endonuclease), resolved by electrophoresis on Agarose-gel (2%) stained with Ethidium bromide at 100volt and 80mA for 90min, and visualized with the UV-transilluminator.

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Table (1): Sequences of primers utilized for SNPs detection for study genes

Reference	Product size	Primer sequence (5′-3′)		Gene
Albegali *et al*. (2019)	221bp	CTTTCCACAGCTCACCTT	F (G allele)	*IRS1*
		GTTAGGCCTGCAAATGTCTA	R (A allele)	
Reddy *et al*. (2021)	349bp	ATGAGCCACCAGGCCATGGCGAAGAG	F:Outer	*KCNJ11*
		AGTGAGGCCCTAGGCCACGTCCGAGG	R:Outer	
	162bp	CTGGCGGGCACGGTACCTGGGATC	F:Inner (C allele)	
	237bp	GACACGCCTGGCAGAGGACCCTGACA	R:Inner (T allele)	
Baqer and Shwan (2023)	453bp	CTCCTAATAGGACAGTGCCAGCCA	F:Outer	*PPARG*
		TTTAAATGAACGCGATAGCAACGAG	R:Outer	
	238bp	GAAACTCTGGGAGATTCTCCTATTGTCC	F:Inner (C allele)	
	267bp	ATCAGTGAAGGAATCGCTTTCAGC	R:Inner (G allele)	
Abdullah and Ali (2022)	429bp	TTTTTCACATGTGAAGACATACAC	F:Outer	*TCF7L2*
		TTTATAGCGAAGAGATGAAATGTA	R:Outer	
	212bp	ATTAGAGAGCTAAGCACTTTTTAGAGA	F:Inner (C allele)	
	269bp	CTCATACGGCAATTAAATTATAGAG	R:Inner (T allele)	

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Table (2): Conditions of Thermal Cycler system for PCR mixture of study genes

Gene				Condition
TCF7L2	***PPARG***	***KCNJ11***	***IRS1***	
1 Cycle (95°C for 5min)	1 Cycle (95°C for 5min)	1 Cycle (95°C for 5min)	1 Cycle (95°C for 5min)	Initial denaturation
35 Cycles (95°C for 30sec)	40 Cycles (95°C for 30sec)	35 Cycles (95°C for 30sec)	35 Cycles (95°C for 30sec)	Denaturation
(62°C for 30sec)	(61°C for 1min)	(61°C for 1min)	(62°C for 30sec)	Annealing
(72°C for 30sec)	(72°C for 45sec)	(72°C for 45sec)	(72°C for 30sec)	Extension
(72°C for 5min)	(72°C for 5min)	(72°C for 5min)	(72°C for 5min)	Final extension
4°C (Forever)	4°C (Forever)	4°C (Forever)	4°C (Forever)	Hold

Statistical analysis

All calculations were done with chi-sqaire (x^2), one-way ANOVA and 95% confidence interval (95%CI) using the GraphPad Prism software; odds ratio (OR), relative risk (RR) and number needed to treat (NNT) were calculated with the MedCalc statistical software. The frequency of the genotypes and alleles among the study populations is significantly different at $p<0.05$ (Gharban et al., 2024).

Results

***IRS1*-rs1801278*G>A* polymorphism**

In OT2DM individuals, the findings shown a significant increase ($p<0.05$) in frequency of GA (65.52%) and AA (83.33%) genotypes with a significant decrease in GG genotype (38.18%) when compared to OND population (34.48%, 16.67%, and 61.82%, respectively). Subsequently, the risk of GA

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and AA genotypes in OT2DM were markedly ($p<0.0001$) higher than OND individuals (Tables 1, 2).

Table (1): Genotype frequency of *IRS1*-rs1801278 *G>A* among the OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Genotype
100.2 to 200.2	0.0363	34 (61.82%)	21 (38.18%)	55	GG
147.2 to 247.2	0.0214	10 (34.48%)	19 (65.52%)	29	GA
373.5 to 473.5	0.0013	1 (16.67%)	5 (83.33%)	6	AA
-	-	0.0402	0.0144	p-value	
-	-	18.84 to 94.15	5.849 to 118.8	95%CI	

Table (2): Risk of genotype frequency of *IRS1*-rs1801278*G>A* among the OT2DM and OND populations

95%CI	NNT	RR	OR	OND	OT2DM	Total	Genotype
35.290 (Harm) to ∞ to 3.457 (Benefit)	7.665 (Benefit)	0.6793	0.2831	34	21	55	GG
3.812 (Harm) to ∞ to 14.634 (Benefit)	10.311 (Harm)	1.3245	2.5577	10	19	29	GA
2.371 (Harm) to ∞ to 6.335 (Benefit)	7.578 (Harm)	1.4091	5.5	1	5	6	AA
-	-	0.0001	0.0001	p-value			
-	-	0.146	3.717	95%CI			

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		to 2.129	to 9.278	

Additionally, though the frequency of G allele was differed insignificantly (p<.0702) between OT2DM (47.62%) and OND (52.38%) populations, significant higher frequency (p<0.0334) of A allele (68.57%) was observed in OT2DM when compared to those of OND (52.38% and 31.43%, respectively). Also, the risk (OR, RR) of A allele in OT2DM (2.4, 1.2610) was significantly higher (p<0.0001) than G allele (0.4167, 0.7930), (Tables 3, 4).

Table (3): Allele frequency of *IRS1*-rs1801278*G*>*A* among the OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Allele
-19.76 to 80.24	0.0702	44 (52.38%)	40 (47.62%)	84	G
186.0 to 286.0	0.0334	11 (31.43%)	24 (68.57%)	35	A
-	-	0.0455	0.0442	p-value	
-	-	91.19 to 175.0	75.00 to 191.2	95%CI	

Table (4): Risk of Allele frequency of *IRS1*-rs1801278*G*>*A* among the OT2DM and OND populations

95%CI	NNT	RR	OR	OND	OT2DM	Total	Allele
15.842 (Harm) to ∞ to 4.319 (Benefit)	11.877 (Benefit)	0.7930	0.4167	44	40	84	G
4.319 (Harm) to ∞ to 15.842 (Benefit)	11.877 (Harm)	1.2610	2.4	11	24	35	A
-	-	0.0001	0.0001	p-value			
-	-	1.946	11.19	95%CI			

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		to 4	to 14.01	

***KCNJ11*- rs5219*C>T* polymorphism**

In *KCNJ11* gene, the frequency of CT genotype (70%) was significantly higher ($p<0.05$) than the CC (36.54%) and TT (62.5%) in OT2DM individuals as well as genotypes of OND population; CC (63.46%), CT (30%) and TT (37.5%). Subsequently, the risk (OR, RR) of CT genotype (3.5, 1.4412) was apparently ($p<0.0001$) higher than those of CC (0.2657, 0.6587) and TT (1.7500, 1.1731) genotypes in individuals of T2DM (Tables 5, 6). Also, the frequency and risk of T allele (68.42%, 2.275, 1.2391) was significantly ($p<0.05$) higher than those of C allele (48.78%, 0.4396, 0.8071) in OT2DM individuals (Tables 7, 8).

Table (5): Genotype frequency of *KCNJ11*-rs5219*C>T* in OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Genotype
121.0 to 221.1	0.0343	33 (63.46%)	19 (36.54%)	52	CC
204.1 to 304.1	0.0268	9 (30%)	21 (70%)	30	CT
108.8 to 208.8	0.0341	3 (37.5%)	5 (62.5%)	8	TT
-	-	0.0111	0.0201	p-value	
-	-	0.0363 to 87.27	12.73 to 99.96	95%CI	

Table (6): Risk of *KCNJ11*-rs5219*C>T* in OT2DM and OND populations

95%CI	NNT	RR	OR	OND	OT2DM	Total	Genotype
52.95 (Harm) to ∞ to 3.376 (Benefit)	7.213 (Benefit)	0.6587	0.2657	33	19	52	CC
3.464 (Harm) to	7.933 (Harm)	1.4412	3.5	9	21	30	CT

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∞ to 27.335 (Benefit)							
3.066 (Harm) to ∞ to 4.703 (Benefit)	17.622	1.1731	1.7500	3	5	8	TT
-	-	0.0001	0.0001	p-value			
-	-	0.1032 to 2.079	5.194 to 10.79	95%CI			

Table (7): Allele frequency of *KCNJ11*-rs5219*C*>*T* in OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Allele
-34.50 to 65.50	0.0855	42 (51.22%)	40 (48.78%)	82	C
184.0 to 284.0	0.0331	12 (31.58%)	26 (68.42%)	38	T
-	-	0.0362	0.0405	p-value	
-	-	83.37 to 166.2	66.17 to 183.4	95%CI	

Table (8): Risk of Allele frequency of *KCNJ11*-rs5219*C*>*T* in OT2DM and OND populations

95%CI	NNT	RR	OR	OND	OT2DM	Total	Allele
15.17 (Harm) to ∞ to 4.491 (Benefit)	12.758 (Benefit)	0.8071	0.4396	42	40	82	C
4.491 (Harm) to ∞ to 15.17 (Benefit)	12.758 (Harm)	1.2391	2.275	12	26	38	T
-	-	0.0001	0.0001	p-value			

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-	-	1.721 to 3.768	10.3 to 13.02	95%CI

***PPARG*-rs1801282 *G>C* polymorphism**

The findings of *PPARG* gene polymorphism were revealed a significant increases ($p<0.05$) in percentage of GC (61.11%) and CC (66.67%) genotypes when compare to GG genotype (37.78%) in the OT2DM population as well as to those of GC (38.89%) of OND individuals. However, the risks (OR, RR) of GC genotype (2.1180, 1.2699) followed by CC genotype (2.1538, 1.2308) in OT2DM population were significantly ($p<0.0001$) higher than identified in GG genotype (0.3686, 0.7149) of OT2DM population (Tables 9, 10). For allele frequency, the results were showed a significant elevation ($p<0.05$, $p<0.0001$) in existence and risk of C allele (62.22%, 1.7738, 1.1336) in comparison with those detected in G allele (48.15%, 0.5638, 0.8473) of OT2DP population as well as when compared to the results of the OND individuals, G (51.85%) and C (37.78%) alleles (Tables 11, 12)

Table (9): Genotype frequency of *PPARG*-rs1801282 *G>C* in OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Genotype
105.3 to 205.3	0.0353	28 (62.22%)	17 (37.78%)	45	GG
91.17 to 191.2	0.0371	14 (38.89%)	22 (61.11%)	36	GC
161.8 to 261.8	0.0306	3 (33.33%)	6 (66.67%)	9	CC
-	-	0.0369	0.0212	p-value	
-	-	6.734 to 82.89	17.11 to 93.27	95%CI	

Table (10): Risk of genotype frequency of *PPARG*-rs1801282 *G>C* in OT2DM and OND populations

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95%CI	NNT	RR	OR	OND	OT2DM	Total	Genotype
20.352 (Harm) to ∞ to 3.733 (Benefit)	9.143	0.7149	0.3686	28	17	45	GG
4.155 (Harm) to ∞ to 12.586 (Benefit)	12.406 (Harm)	1.2699	2.1180	14	22	36	GC
3.051 (Harm) to ∞ to 5.627 (Benefit)	13.333 (Harm)	1.2308	2.1538	3	6	9	CC
-	-	0.0001	0.0001	p-value			
-	-	0.3024 to 1.841	0.9883 to 4.082	95%CI			

Table (11): Allele frequency of *PPARG*-rs1801282*G>C* in OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Allele
-26.49 to 73.51	0.0775	42 (51.85%)	39 (48.15%)	81	G
105.3 to 205.3	0.0353	17 (37.78%)	28 (62.22%)	45	C
-	-	0.021	0.0203	p-value	
-	-	44.57 to 134.2	34.20 to 144.6	95%CI	

Table (12): Risk of Allele frequency of *PPARG*-rs1801282*G>C* in OT2DM and OND populations

95%CI	NNT	RR	OR	OND	OT2DM	Total	Allele

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12.548 (Harm) to ∞ to 5.081 (Benefit)	17.076 (Benefit)	0.8473	0.5638	42	39	81	G
5.569 (Harm) to ∞ to 10.784 (Benefit)	23.03 (Harm)	1.1336	1.7738	17	28	45	C
-	-	0.0001	0.0001	p-value			
-	-	0.8284 to 2.809	6.518 to 8.856	95%CI			

***TCF7L2*-rs7903146 *C>T* polymorphism**

The polymorphism results of the *TCF7L2* gene identified that the frequency of CT (64.1%) and TT (66.67%) genotypes in OT2DM population was significantly higher ($p<0.05$) than detected in OND (35.9% and 33.33%, respectively); whereas, frequency rate of CC genotype was reduced significantly ($p<0.0431$) in OT2MD population (35.56%) compared to those of OND individuals (64.44%), (Tables 12, 13).

Table (12): Genotype frequency of *TCF7L2*-rs7903146*C>T* among the OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Genotype
133.5 to 233.5	0.0431	29 (64.44%)	16 (35.56%)	45	CC
129.2 to 229.2	0.0435	14 (35.9%)	25 (64.1%)	39	CT
161.8 to 261.8	0.0301	2 (33.33%)	4 (66.67%)	6	TT
-	-	0.0466	0.0308	p-value	
-	-	1.662 to 87.45	12.55 to 98.34	95%CI	

Table (14): Risk of genotype frequency of *TCF7L2*-rs7903146*C>T* among the OT2DM and OND populations

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95%CI	NNT	RR	OR	OND	OT2DM	Total	Genotype
34.861 (Harm) to ∞ to 3.474(Benefit)	7.716 (Benefit)	0.6693	0.3044	29	16	45	CC
3.744 (Harm) to ∞ to 20.301 (Benefit)	9.18 (Harm)	1.3867	2.7679	14	25	39	CT
2.2664 (Harm) to ∞ to 4.322 (Benefit)	13.889 (Harm)	1.2195	2.0976	2	4	6	TT
-	-	0.0001	0.0001	p-value			
-	-	0.1594 to 2.024	1.441 to 4.887	95%CI			

Concerning the allele frequency of the *TCF7L2* gene, the findings reported a significant elevation (p<) in percentage and risks (OR, RR) of T allele (64.44%, 1.6008, 1.1948, respectively) when compared to C allele (48.81%, 0.5261, 0.837, respectively) in the OT2MD population as well as when compared to C (51.19%) and T (35.56%) alleles in OND individuals (Tables 15, 16).

Table (15): Allele frequency of *TCF7L2*-rs7903146*C>T* among the OT2DM and OND populations

95%CI	p-value	OND	OT2DM	Total	Allele
-34.88 to 65.12	0.0859	43 (51.19%)	41 (48.81%)	84	C
133.5 to 233.5	0.0231	16 (35.56%)	29 (64.44%)	45	T

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-	-	0.0437	0.0237	p-value
-	-	55.92 to 142.7	42.67 to 155.9	95%CI

Table (16): Risk of Allele frequency of *TCF7L2*-rs7903146*C>T* among the OT2DM and OND populations

95%CI	NNT	RR	OR	OND	OT2DM	Total	Allele
13.68 (Harm) to ∞ to 4.978 (Benefit)	15.651 (Benefit)	0.837	0.5261	43	41	84	C
4.978 (Harm) to ∞ to 13.68 (Benefit)	15.651 (Harm)	1.1948	1.6008	16	29	45	T
-	-	0.0001	0.0001	p-value			
-	-	1.257 to 3.289	5.764 to 7.891	95%CI			

Discussion

Several genes have been the focus of significant research in the past 10 years, because they may play a role in regulating insulin signaling pathways and, therefore, be responsible for an individual's susceptibility to T2DM in particular, in an obese population. In the current study, *IRS1* rs1801278*G>A* revealed higher frequency of GA and AA genotype and a significantly lower frequency of GG genotype in the OT2DM group indicating that the A allele (Arg972 variant) of the IRS1 gene is crucial in enhancing T2DM susceptibility among obese individuals. Our results were similar to the findings of other international (Tang et al., 2015) and national (Mudhaffer and Hassan, 2025) who found that IRS1- rs1801278 polymorphism was associated with increased risk of T2DM, but were not found to be associated with insulin resistance and other related metabolic parameters in overweight

and obese individuals with T2DM in other studies (Htwe et al., 20221; Rasool et al., 2022; Shen et al., 2024). A few evidences suggest that substitution of glycine with arginine at codon 972 could change the structure of IRS1 protein, which will inhibit the interaction with key downstream signaling molecules like PI3K and AKT and thus disrupt insulin signaling pathway and contribute to insulin resistance (Khalid et al., 2021; Pei et al., 2022; Báez et al., 2024). Further studies also noted that the amino acid change in the *IRS1* gene caused by the rs1801278 polymorphism may compromise insulin downstream signaling pathways, leading to insulin resistance (Niyasti et al., 2022; Luo et al., 2023; Sarvestani et al., 2023; Mudhaffer and Hassan, 2025). Islam et al. (2024) noted that the G>A transition of the genetic variant of *IRS1*, rs1801278, has been associated with changes in insulin sensitivity and glucose homeostasis, suggesting that further research in this field is warranted to identify targeted strategies for personalized risk assessment and treatment. Further, the interaction of this polymorphism with environmental risk factors like obesity provides insights into the mechanism by which diabetes develops in at-risk individuals (Gupta et al., 2024). Taken together, the last reports show that the variant IRS1 rs1801278 is a plausible and clinically relevant risk factor for T2DM, specifically in the genetically susceptible and obese population (Danyarova et al., 2026; Hryniewicka et al., 2026; Pal et al., 2026).

In this study, analysis of the *KCNJ11*-rs5219*C>T* polymorphism gene detected that the frequency of CT genotype was significantly higher than the CC and TT in OT2DM and OND populations with marked increasing the percentage and risk of T allele compared to C allele. These results indicated that the polymorphism was a possible genetic risk factor for the disease in this population. The finding is consistent with the previous and recent studies reporting importance of the *KCNJ11* gene in regulation of insulin secretion and its polymorphisms association with susceptibility to T2DM among different populations (Phani et al., 2014; Haghvirdizadeh et al., 2015; Ageeva et al., 2024; Pati et al., 2025). This effect of *KCNJ11* gene might be attributed to its role in encoding and synthesis of Kir6.2 proteins that act as a

fundamental component in ATP-sensitive potassium channel in pancreatic beta cells (Ramteke et al., 2024).

The results of this study showed that the percentage of GC and CC genotypes were apparently higher than GG genotype in the OT2DM population and in the GC genotype of the OND. For allele frequency, the results were showed a significant elevation in existence and risk of C allele in comparison with those detected in G allele of OT2DM population as well as when compared to the results of the OND individuals, G and T alleles. These results were similar with that recorded by other studies concluded additionally that the G allele of the rs1801282 polymorphism confers an increased risk of obesity and hypercholesterolemia (Li et al., 2022; Rani et al., 2025). Worldwide, several previous and recent studies have examined the polymorphism in a context of OT2DM development with findings suggesting that allele frequency is notably increases in diabetic non-obese and diabetic obese patients when compared to control group (Sokkar et al., 2009; Valeeva et al., 2022). However, other previous studies concisely reviewed that this polymorphism does not relate to predisposition of metabolic disorders (Rocha et al., 2015), or offer protection to the development of other diseases like polycystic ovary syndrome (Zhang et al., 2015) and colorectal cancer (Jiang et al., 2017). The complex interplay highlights the need for a detailed understanding of the *PPARG*-rs1801282*G>C* polymorphism's implications in the context of lipid metabolism and adipocyte function, especially in the context of obesity and insulin sensitivity.

In our findings, there was significantly higher allelic frequencies of CT and TT genotype in the population of OT2DM than in OND, whereas, the percentage of T and the risk of T was significantly higher than C in the population of OT2DM and compared to C allele and T allele in OND population. These data were in context that reported by many studies (Assmann et al., 2014; Ding et al., 2018; Lu et al., 2025). The molecular mechanisms behind this association include increased *TCF7L2* mRNA expression in pancreatic islets of T allele carriers, which results in reduced insulin secretion, decreased incretin effects and increased production of

hepatic glucose (Bahaaeldin et al., 2020). On the other hand, the relationship between the C allele of *TCF7L2*- rs7903146 and obesity is less well explored in the literature and requires further investigations for its replication in other diversified populations (Sen et al., 2025).

Conclusion

This study indicates the predominant and risk of *IRS1G>A* (rs1801278), *KCNJ11C>T* (rs5219), *PPARGG>C* (rs1801282), and *TCF7L2C>T* (-rs7903146) in OT2DM patients. This suggests that furthermore studies are necessary to investigate the roles of various genes in OT2DM, and possible utilization of such genes in diagnosis of this metabolic disorder. Also, identifying of *IRS1*, *KCNJ11*, *PPARG*, and *TCF7L2* genes in both obese and non-obese populations can help in understanding of diseases mechanism and supported the preventing healthcare strategies. As precision medicine continuously evolved, combination of genetic information with clinical and lifestyle factors could be greatly managed and reduced the burden of T2DM.

Ethical approval

This study was approved by the Scientific Committee in the Department of Biology (Collage of Science, University of Wasit).

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