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Research Article

KCNJ11 Gene Polymorphism and Its Association with Type 2 Diabetes Mellitus in Iraqi Population

*[1]Raghad Abdulmahdi Naser, [1]Hasanat Abdulrazaq Aljabery

About Article

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About Author

[1] Department of Biochemistry, Faculty of Medicine, University of Kufa, Iraq

Contact @ Raghad Abdulmahdi Naser
raghada.alnajjar@student.uokufa.edu.iq

ABSTRACT

Diabetes mellitus is a complicated metabolic condition marked by hyperglycemia, results in consequences that decrease quality of life and increasing mortality rates. (*KCNJ11*) Potassium inwardly-rectifying channel, subfamily J, member 11 gene mutations can result in susceptibility of T2DM. To verify the correlation between the *KCNJ11* gene single nucleotide polymorphism and the incidence of type 2 diabetes mellitus in Iraqi society. A case-control study involved 150 patients with type 2 diabetes mellitus from the Diabetic Center at Al-Sader Teaching Hospital in Najaf City, Iraq, who were compared to 150 healthy control group. Both groups satisfied the inclusion requirements. Blood was taken from all participants, and standard methodologies were employed to assess fasting blood glucose (FBS), serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and insulin levels. A HOMO-IR calculation was conducted. The *KCNJ11* gene rs1800467 SNP was genotyped using the Polymerase Chain Reaction-Allele Specific (PCR-AS) approach. The GC genotype of the rs1800467 SNP showed significant variation between diabetic and control groups under genetic models (P<0.005). The minor allele frequency of rs1800467C was increased in T2DM patients compared to controls (OR = 5.58, 95% CI = 1.61 – 19.35, P = 0.0039). Single nucleotide polymorphism of the *KCNJ11* gene (rs1800467) is significantly linked with susceptibility to type 2 diabetes mellitus in the Iraqi population.

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1. INTRODUCTION

Diabetes mellitus (DM) describes a group of metabolic disorder characterized by chronic hyperglycemia, resulting from impaired insulin production, insulin action, or a combination of both factors (Yameny, 2024), leading to abnormalities in glucose, protein, and lipid metabolism (Yang *et al*., 2023). Type 2 diabetes mellitus is the main cause of premature death, primarily due to cardiovascular disease (Kaftan *et al*., 2021).

The latest edition of the International Diabetes Federation (IDF) Diabetes Atlas reports that over 500 million individuals globally have diabetes, with predictions suggesting a 20% increase by 2030 and a 46% increase by 2045 (Zhu *et al*., 2024). Chronic hyperglycemia in diabetes mellitus can result in damage, dysfunction, and failure of end organs, including the retina, kidneys, nervous system, heart, and blood vessels (Alam *et al*., 2014). Numerous environmental factors have been associated to obesity that results in type 2 diabetes, including being overweight, eating a high-fat diet, getting older, and not exercising (Hinault *et al*., 2023), Furthermore , a group of candidate genes known as their correlated with type 2 diabetes due to its impact in the development of metabolic disorder (Mashal *et al*., 2021; Wu *et al*., 2014).

2. LITERATURE REVIEW

Numerous Genome Wide Association Studies (GWAS) identified a number of single nucleotide polymorphism (SNP) located in intragenic or intergenic regions have been associated with increased risk of developing type 2 diabetes (Al-Khalayfa *et al*., 2023). All of these SNPs correlated with T2DM have been shown to influence insulin secretion , insulin resistance, and glucose or lipid metabolism (Goyal *et al*., 2019). *KCNJ11* is the most studied of the many genes involved with diabetes (Njølstad *et al*., 2010). *KCNJ11* gene greatly influence insulin activity, glucose metabolism, pancreatic beta cell function, and other metabolic process like energy intake and expenditure, and lipid metabolism (Schwenk *et al*., 2013).

KCNJ11 is a significant candidate gene in the risk of T2DM because of its role in regulating glucose-induced insulin production (Alqadri, 2022). The *KCNJ11* gene is placed onto the short arm of chromosome 11, exactly at 11p15.1. It is a single exon gene of 4.08 Kb (Ghanem *et al*., 2016). The *KCNJ11* gene, which encodes the Kir6.2 subunit belongs to the inward rectifying potassium channel J subfamily. The Kir6.2 (protein) encodes the pore-forming subunit of the ATP-sensitive potassium channel (KATP) in pancreatic beta cells. An increase in the KATP activity in pancreatic beta cells is associated with decreased insulin production, rising fasting plasma glucose levels, impaired pancreatic cell function, and the development of diabetes mellitus (Qin *et al*., 2013).

Studies indicate that *KCNJ11* gene is significantly expressed in pancreatic β-cells (Jiang *et al*., 2017; Isakova *et al*., (2019). Several Polymorphisms have been identified in this gene, including rs1800467 which has been associated with diabetes (Phani *et al*., 2014). However, rs1800467 SNP has not been studied in Iraqi population. current study intends to estimate the relationship of *KCNJ11* rs1800467 polymorphism with T2DM in Iraqi population. Furthermore, it aims to check the effect of the polymorphism on major metabolic parameters such as fasting blood glucose, insulin, lipids, and HOMA-IR.

3. METHODOLOGY

3.1. Study subjects

The present research is a case-control design, comprising 150 adult diabetic patients (the pathological case group) and 150 healthy adult individuals (the control group). The study's period extended from August 2024 to December 2024. Patients were selected from the Al-Najaf Center for Diabetes and Endocrinology, located within Al-Sadr Medical City in the Al-Najaf Governorate.

The diagnosis was done based on the criteria set by American Diabetes Association (ADA), which includes FPG (fasting plasma glucose) ≥126 mg/dL and/or HbA1c ≥6.5%, along with some clinical signs and symptoms. The subjects in the control group were of similar age with no family or personal medical history of diabetes or cardiovascular disease.

The written informed consent was obtained from each volunteer before enrollment in this study. A questionnaire in English languages was also prepared to evaluate demographic information such as gender, age, height, weight, duration of disease, ethnicity, medications, and T2DM family history. The biochemical along with genetic tests were performed in the Postgraduate Laboratory of the Biochemistry Department at the University of Kufa's Faculty of Medicine.

3.2. Biochemical analysis

Five milliliters of blood have been taken from each participant using peripheral venipuncture after an overnight fast. Subsequently, the blood samples were separated into two portions. First portion is three milliliters of blood were placed in a plain tube and permitted to coagulate at 37°C for around 15 minutes, then undergoing centrifugation at 2000 xg for 10-15 minutes. The resultant serum was isolated and preserved at -20°C for the assessment of phenotypic characteristics. Second portion is two milliliters of blood were mixed with EDTA in a tube for genetic analysis.

Weight (kg) and height (m) measurements were performed utilizing established procedures, and the Body Mass Index (BMI) was calculated using the formula weight (kilograms) divided by the square of height (meters). The biochemical parameters tested included serum insulin using enzyme linked immunosorbent assay (ELISA), while triglycerides (TG), cholesterol, and high-density lipoprotein (HDL) levels were evaluated using established enzymatic methods. Levels of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were determined by mathematical methods.

3.3. Genotyping analysis

DNA is extracted from blood via a DNA purification mini kit (Geneaid). The quality and concentration of DNA have been confirmed with a BioDrop spectrophotometer, by evaluating the A260/A280 ratio (ideal range 1.6 – 1.8) and the 260/230 ratio (2.0–2.2), to confirm purity (Lucena-Aguilar *et al*., 2019).

KCNJ11 polymorphism (rs1800467) was genotyped utilizing polymerase chain reaction-allele specific (PCR-AS). The DNA sample was amplified using the following primers: Forward primer: AGTAACGTCCGTCCTCCTCA,

Allele G: CAACAGCCCACTCTACGACC, Allele C: CAACAGCCCACTCTACGACG and the PCR products were analyzed on 2.5% agarose gel (60 minutes at 75V) and subsequently visualized under UV light.

The presence or absence of a specific PCR product represents the presence or absence of the corresponding allele. Amplification was performed utilizing 2 PCR tubes in a total reaction volume of 25 µl in each tube the following component: tube one contains 12.5 µl GoTaq Green Master Mix (Promega, U.S.A), 2 µl of reverse primer, 2 µl of allele G primer, 2.5 µl of nuclease free water, and 6 µl genomic DNA solution as template.

Tube two contains 12.5 µl GoTaq Green Master Mix (Promega, U.S.A), 2 µl of reverse primer, 2 µl of allele C primer, 2.5 µl of nuclease free water, and 6 µl genomic DNA solution as template. The PCR reaction program was; 95 °C for 5 min followed by 35 cycles of 95 °C for 30s, 61 °C for 30 s, 72 °C for 1 min. and a final extension at 72 °C for 7 min. The amplification product of rs1800467 SNP was 191 bp for allele G and allele C, analyzed on 2.5% agarose.

3.4. Statistical analysis

Continuous variable data were presented as mean ± standard deviation (SD). The t-test was applied to compare the control group with the diabetes group, whilst the ANOVA test was implemented to compare numerical data across many groups. Statistical significance was assessed utilizing SPSS version 26.0 software (SPSS Inc., Chicago, IL). The Chi-squared test (x^2) was utilized to assess differences in genotyping and allele frequencies between the diabetes group and the control group. Age and gender adjustments were performed for the calculation of odds ratios (OR), confidence intervals (CI95%), and P-values. A significance level of < 0.05 was used to evaluate significant results.

3.5. Ethical approval

The present study which is conducted by (RAM, HAR) is approved by the scientific committee of the Department of Biochemistry, College of Medicine. University of Kufa, Iraq.

4. RESULTS AND DISCUSSION

4.1. Baseline characteristics of the study population

Anthropometric and biochemical results as shown in Table 1. The comparison of ages and BMI values in the patients group versus the control group revealed non-significant variations according to the P-value (0.077) and (0.617) for age and BMI, respectively. Other parameters were found to change in T2DM patients when compared with healthy individuals. Levels of TG, TC, VLDL-C, LDL-C, FBG, insulin, and HOMA-IR exhibited significant increase (p<0.001) in the patient's group when compared with the group of control. Nevertheless, HDL-C levels exhibited significant reduction (P < 0.008) in T2DM patients when compared with the control group.

Table 1. Anthropometric and biochemical factors values of T2DM and control

Parameters	Control Mean ± SD	T2DM Mean ± SD	P-value
No (M/F)	150 (71/79)	150 (67/83)	
Age (y)	50.65 ± 6.48	52.16 ± 8.18	0.077
BMI (Kg/m2)	29 ± 5.17	29.31 ± 5.34	0.617
TG (mg/dl)	114.99 ± 12.72	241.95 ± 35.39	0.001
TC (mg/dl)	145 ± 22.7	251 ± 24.2	0.001
VLDL-C (mg/dl)	24.61 ± 4.68	47.29 ± 10.90	0.001
LDL-C (mg/dl)	97.10 ± 12.51	152.58 ± 10.29	0.001
HDL-C (mg/dl)	43.86 ± 8.62	41.39 ± 7.31	0.008
FBG (mg/dl)	93.83 ± 8.63	168.67 ± 26.24	0.001
Insulin (µU/L)	6.38 ± 5.23	11.61 ± 6.92	0.001
HOMA-IR	1.49 ± 1.38	4.80 ± 2.89	0.001

4.2. Distribution of genotypic and allelic frequencies of *KCNJ11* rs1800467 variant

The amplification of the *KCNJ11* gene was performed using template DNA and specific primers with a master mix. The product of PCR was electrophoresed on 2.5% agarose (60 min at 75V) and immediately visualized under the UV light. The amplification product of *KCNJ11* gene SNP rs1800467 G/C was found to be 191bp (Allele G and Allele C), as shown in Figure 1. The *KCNJ11* rs1800467 polymorphism genotype distribution and allele frequencies for both groups (T2DM patients and control subjects) are presented in Table 2. In different genetic models (codominant, dominant, and additive model) showed significant variation between the two groups as well as the frequency of C allele showed highly significant difference.

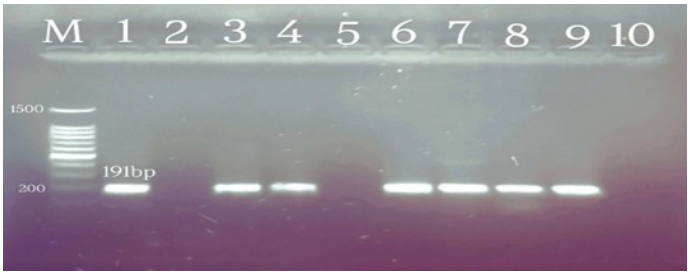

Figure 1. Genotyping of rs1800467 SNP by electrophoresis on 2.5% agarose. M is ladder of DNA (1500 bp). Lanes 1 and 9 showed GG genotype (191 bp). Lanes 3, 4, 7, and 8 showed GC genotype (191 bp). Line 6 showed CC genotype (191 bp).

Table 2. Genotype and allele frequency of rs1800467 SNP in the *KCNJ11* gene in T2DM and control subjects.

Genotyping	Control N=150(%)	Patient N=150(%)	OR 95%CI	P-value
Codominant				
G / G	147 (98%)	136 (90.7%)	Ref.	0.014
G / C	3 (2%)	12 (8%)	4.28 (1.16-15.74)	
Dominant				
G / G	147 (98%)	136 (90.7%)	Ref.	0.0051
G / C - C / C	3 (2%)	14 (9.3%)	4.97 (1.39-17.84)	
Additive				
G / G – C / C	147 (98%)	138 (92%)	Ref	0.015
G / C	3 (2%)	12 (8%)	4.29 (1.16-15.77)	
Allele				
G	297 (99%)	284 (95%)	Ref	0.0039
C	3 (1%)	16 (5.3%)	5.58 (1.61-19.35)	

Table 3. Phenotypic parameters and their association with rs1800467 genotypes among diabetic patients

Characteristic	GG N=136	G/C N=12	CC N=2	P value
BMI	29.32 ± 5.40	29.82 ± 4.80	25.15 ± 4.74	0.585
FBG	168.41 ± 26.08	169.92 ± 28.33	179 ± 41.01	0.940
Cholesterol	252.28 ± 25.58	245.67 ± 30.59	256.50 ± 17.68	0.787
TG	244.27 ± 33.99	220.75 ± 45.13	211.50 ± 14.85	0.128
HDL-C	41.65 ± 7.43	37.50 ± 4.64	47 ± 4.24	0.131
LDL-C	152.62 ± 10.45	151.33 ± 9..37	157.50 ± 3.54	0.342
VLDL-C	47.68 ± 10.91	42.83 ± 10.89	47.50 ± 7.78	0.515
Insulin	11.68 ± 7.10	10.55 ± 5.06	13.20 ± 3.96	0.736
IR	4.82 ± 2.96	4.41 ± 2.17	6.03 ± 3.09	0.776

4.3. Discussion

The current study is the first in our knowledge to demonstrate the association between the *KCNJ11* rs1800467 polymorphism and susceptibility to T2DM in the Iraqi population. Our findings indicate a significantly increased frequency of the C allele rs1800467 with heterozygous genotype (GC) in T2DM patients when compared with healthy controls.

The significant associations of the GC genotype of the rs1800467 SNP with a 4.28-fold elevated risk of type 2 diabetes mellitus occurrence were observed as presented in Table 2. Our results aligned with previous research, such as the study conducted by Chan *et al.* (2015)which indicated that the rs1800467 polymorphism in *KCNJ11* was strongly associated with an increased risk of T2DM, presenting a 2.50-fold risk for its development (Chan *et al.*, 2015). Two previous studies have detected *KCNJ11* as a significant susceptibility loci for T2DM (Aguilar-Bryan & Bryan, 1999; Edghill *et al.*, 2010). Additionally, *KCNJ11* polymorphism rs1800467 (L270V) is a common missense polymorphism that has been noticed to effect the risk of T2D in several studies (Tarasov *et al.*, 2008; Hansen *et al.*, 2005; Florez *et al.*, 2004).Contrary to our findings, a study indicated no difference in the genotypic and allelic frequencies of the *KCNJ11* gene L270V variation between diabetes and non-diabetic individuals (Phani *et al.*, 2014). Incompatible outcomes may arise from variations in ethnicities, genetic roots of the study population, and geographic differences.

The *KCNJ11* gene plays an important role in the regulation of glucose-induced insulin secretion (Perwitasaria *et al.*, 2020). It offers instructions for making subunits of the ATP-sensitive potassium (K-ATP) channel (Althwanay *et al.*, 2020). K-ATP channels are located in beta cells, which are cells in the pancreas that produce the insulin hormone. The K-ATP channels are found within cell membranes, regulating their opening and closing in accordance to blood glucose levels (Perwitasaria *et al.*, 2020). Closure of the K-ATP channels due to elevated glucose levels stimulates the secretion of insulin from beta cells into the bloodstream, hence regulating blood sugar levels (Bennett *et al.*, 2010). The rs1800467 (L270V) polymorphism is a missense mutation (C-G substitution) found on chromosome 11, leading to amino acid alteration from Leu / CTG to Val / GTG at codon 270 (Boodram *et al.*, 2011).

The association between the SNP of L270V in the *KCNJ11*gene

and the demographic risk factor of the study population was also investigated in our study. No relationship was noticed between biochemical parameters and genotyping of the rs1800467 SNP between T2DM patients as shown in Table 3. The results are consistent with data achieved from meta-analysis research in T2DM patients (Phani *et al.*, 2014).

The present study has some limitations, including a small sample size and a study power of 75%. Consequently, future research need investigations with an adequate sample size including all Iraqi states that confirm the existing findings.

5. CONCLUSION

The results of the present study showed that Polymorphisms in *KCNJ11* gene rs1800467 SNP was associated with increased risk of T2DM in Iraqi population. There was no association between rs1800467 (L270V) SNP with metabolic parameters.

Future research should

• Replicate in larger, multi-center Iraqi cohorts with adequate power and inclusion of major ethnic groups (e.g., Arab, Kurdish, Turkmen). Control for population stratification using ancestry-informative markers and principal components. Follow STREGA reporting guidelines.

• Extend beyond single-SNP analyses. Perform haplotype analysis across *KCNJ11*–ABCC8 (KATP channel locus), investigate gene–gene interactions with established T2DM loci (e.g., TCF7L2, KCNQ1, FTO, PPARG), and develop/validate Iraqi-specific polygenic risk scores.

• Conduct longitudinal studies to assess the predictive value of *KCNJ11* variants for incident T2DM, progression from prediabetes, and development of complications, with stratification by age, sex, BMI, and family history.

• Evaluate gene–environment interactions relevant to Iraq (dietary patterns, physical activity, smoking, urban/rural residence) and gene–drug interactions, particularly with sulfonylureas, to inform pharmacogenetic applications.

• Perform functional studies (e.g., electrophysiology of Kir6.2/KATP, insulin secretion assays) to clarify the biological impact of common variants (such as E23K/rs5219) observed in the Iraqi population.

• Explore clinical subgroups: early-onset T2DM, lean T2DM, gestational diabetes mellitus, and differential risk of microvascular/macrovascular complications by genotype.

• Build Iraqi reference panels (through local whole-genome sequencing) and contribute allele frequency data to international repositories to improve imputation accuracy and cross-population comparability.

• Pre-register protocols, use standardized phenotyping (OGTT, HOMA-IR, lipid profile), ensure rigorous QC of genotyping/sequencing, and enable data sharing under appropriate ethical safeguards.

These steps will help clarify the role of *KCNJ11* polymorphisms in T2DM risk within the Iraqi population and determine whether and how such information can be responsibly translated into improved prevention and care.

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