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KCNQ1 Variant rs2237892 Linked with Type 2 Diabetes in Yemeni Individuals

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Abstract

Introduction: The pathophysiology of type 2 diabetes mellitus involves both resistance to insulin and insufficient insulin secretion by the pancreatic β-cell. According to earlier genomic studies, T2D is associated with slight changes in single-nucleotide polymorphisms (SNPs) essential for insulin release. The study aimed to investigate the correlation between T2D with a specific genetic variant (SNP) in the KCNQ1 gene, known as rs2237892, among Yemeni people.
Method: In a case-control study, an allelic discrimination assay and TaqMan Real-Time PCR technology were used to genotype 150 Yemeni adults with diabetes and 150 without it.
Results: Triglyceride, total cholesterol, and LDL-C levels were significantly higher in the T2D group compared to healthy controls ($P < 0.001$). After adjusting the age and BMI, neither the dominant nor the additive genetic models showed a statistically significant association with T2D (OR = 0.335, P = 0.153; OR = 1.489, P = 0.15, respectively). However, the recessive genetic model for the KCNQ1 SNP rs2237892 demonstrated a significant association with T2D among Yemeni individuals (OR = 2.69, P = 0.01).
Conclusion: This study identifies a significant correlation between the recessive model of KCNQ1 rs2237892 polymorphism and T2D susceptibility among Yemeni individuals

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INTRODUCTION

Over the past three decades, the number of cases of diabetes mellitus worldwide has doubled, making it a serious public health concern [1]. Diabetes is the term used to describe high blood glucose levels brought on by changes in physiological function or insufficient insulin production [2]. From an estimated 537 million in 2021 to 643 million in 2030 and 783 million in 2045, the incidence of diabetes is expected to rise by over 46% [3]. Diabetes is expected to become much more common in middle-income areas using both low- and high-profit international platforms. Type 1 diabetes affected 8.4 million people worldwide in 2021, including 1.5 million people under the age of 20. 13.5–17.4 million people are expected to have type 1 diabetes by 2040, which is a 60%–107% rise from 2021 [4]. Approximately 80% of all instances of type 2 diabetes mellitus (T2DM) are found in low- and middle-income countries, although prevalence varies significantly by location [5]. The rising prevalence of diabetes in the Middle East is being exacerbated by several variables, including genetic predisposition, urbanization, and physical inactivity linked to obesity. Among Middle Eastern countries, Kuwait, Qatar, and Egypt had the highest rates of diabetes prevalence between 2000 and 2014 [6]. The 22 Arab nations—Bahrain, Qatar, United Arab Emirates, Kuwait, Oman, Saudi Arabia, Algeria, Egypt, Iraq, Jordan, Lebanon, Libya, Comoros, Djibouti, Mauritania, Morocco, Palestine, Somalia, Sudan, Syria, Tunisia, and Yemen—exhibit significant diversity in geography and socioeconomic status [7]. Research on diabetes mellitus has been limited in Yemen. A 2019 observation states that 9.8% of Yemeni men were affected

to DM [8]. The overall prevalence of type II diabetes in Yemen increased to 4.6% in 2004, with 2% of women and 7.4% of men afflicted with the condition [9]. Type 2 diabetes mellitus (T2DM) accounts for 85 to 95 percent of all diabetes cases, representing a significant hyperglycemic condition. It is characterized by compensatory hyperinsulinemia, marked by reduced sensitivity of peripheral tissues to plasma insulin and a gradual decline in the pancreatic β-cells' ability to sustain glucose homeostasis [10]. Insulin is released as a result of the pancreatic β cells' quick ion exchanges. The pancreatic β cells' internal K+ levels rise when the ATP-sensitive potassium (KATP) channel closes, allowing more Ca2+ to enter and aiding in the production of insulin [11]. Worldwide, 463 million individuals between the ages of 20 and 79 have diabetes, mainly type 2 diabetes, according to the ninth edition of the Global Diabetes Map, which was created with support from IDF-2019. By 2030, 578 million individuals are expected to have diabetes, and by 2045, that number is expected to increase to 700 million cases [12]. Type 2 diabetes and its consequences harm residents. Several genome-wide association studies (GWAS) have revealed potential loci that increase an individual's risk of type 2 diabetes. Genome-wide association studies suggest that KCNQ1 is a particular gene linked to an elevated risk of type 2 diabetes, although the exact cause of the disease is unknown [13]. The KCNQ1 gene is found on chromosome 11p15 and is a member of the KQT-like subfamily Q, which includes voltage-gated potassium channels. Five methods were employed to encode the protein. [14]. KCNQ1 inhibitors may increase insulin production by 293B by blocking the channel, indicating that KCNQ1 is involved in insulin release [15]. The KCNQ1 gene rs2237892, located in intron 15, is the most important SNP linked to the risk of T2D [16]. The connection between type 2 diabetes and the single-nucleotide polymorphism (SNP) rs2237892 in the KCNQ1 gene was studied in Yemeni individuals.

MATERIALS AND METHODS

Data Collection and Subjects

This study was a case-control study involving 300 subjects aged 30 to 70 years: 150 were healthy individuals with out a history of diseases such as diabetes, renal disease, liver disease, or cancer, serving as the control group, while the remaining 150 were T2D attending the outpatient clinic of the National Diabetic Centre at Al-Thawra Hospital, Al-Gumhori Teaching Hospital Authority, and the National Center of Public Health Laboratories (NCPHL) in Sana'a, Yemen, during 2024. The Sana'a University Faculty of Medicine and Health Sciences' Institutional Review Board (IRB) gave its approval to the study's procedure. After describing the study's goals and methods, we made sure to have everyone's signed informed consent forms. A battery of biochemical and clinical tests was administered to every individual who took part. The following were part of the criteria for inclusion in the study: subjects had to be Yemeni, aged 30-70, have no first-degree relatives with diabetes, and have a fasting glucose value of less than 6.1 mmol/L, as per the 2006 World Health Organization criteria. Additionally, they could not have any chronic diseases, including heart failure, chronic kidney disease, cancer, liver disease, or endocrine disease.

Sample collection and DNA extraction

A venous blood sample of five mL was obtained from each individual following an overnight fast of over ten hours. The collected blood was immediately taken into two labelled Vacutainer tubes, the first one plain tube without any anticoagulants was for biochemical assay, the second tubes containing K2EDTA was for DNA extraction and glycated hemoglobin (HbA1c), For biochemical analysis, the serum from each sample was separated within 30 minutes, aliquoted into Eppendorf tubes, and promptly stored at -20°C.

DNA extraction was done within 4 hours of blood collection and frozen at -80°C for genetic analysis.

Biochemical Analyses

Measurement of blood glucose, HbA1c, insulin, creatinine, lipid profile, total cholesterol, triglycerides, high-density lipoprotein (HDLc), and low-density lipoprotein (LDLc) was performed at the National Center of Public Health Laboratories (NCPHL), Sana'a City, using Beckman-Coulter analyzers USA.

DNA Isolation and Genotyping

The standard salting-out method was employed to isolate genomic DNA from a 3 mL sample of EDTA blood [17]. The concentration and purity of the extracted DNA were determined using a nanodrop spectrophotometer (JENWAY- Genova Nano, Thermo Fisher Scientific, USA) at wavelengths 260-280 nm. Genotypic analysis was conducted on single-nucleotide polymorphisms of KCNQ1 (rs2237892) in Yemeni T2D patients. Genotyping was conducted using a QuantStudio real-time polymerase chain reaction instrument (Applied Biosystems, United States) and the allelic discrimination assay-by-design TaqMan method. This SNP was amplified using a 96-well plate in a thermocycler (Real-Time PCR Systems, Quant Studio Applied Biosystems Inc., Foster City, CA, USA). Allele labeling was conducted using the PCR software for SNP genotyping (Applied Biosystems, Foster City, California).

Table 1. Anthropometric and biochemical analysis.

Parameters		T2DM group N (150)	non diabetic group N (150)	*P*- value
Sex	Male	73 (48.7%)	58 (38.7%)	0.081
	Female	77 (51.3%)	92 (61.3%)	
Age (years)		53.57 (52.09- 55.03)	49.96 (48.49- 51.42)	<0.001
Height (cm)		159.3 (158.1-160.6)	158.8 (157.5 -65.37)	0.598
Weight (kg)		67.86 (66.20- 69.53)	63.707(62.04- 67.03)	<0.001
BMI (kg/m^2)		27.02 (26.50- 27.53)	24.19) 23.67- 24.69)	<0.001
FBS (mmol/L)		7.60 (7.24 -7.97)	4.43 (4.21 - 4.64)	<0.001
HbA1c (%)		7.95 (7.72-8.19)	4.60 (4.36 - 4.83)	<0.001
TG (mg/dl)		184.8 (172.3-197.4)	135.5 (123.04-148.13)	<0.001
Total cholesterol (mg/dl)		181.05 (173.4 -188.6)	160.6 (153.1-168.2)	<0.001
HDL cholesterol (mg/dl)		35.6 (34.1- 37.2)	36. 9 (35.4- 38.4)	0.267
LDL cholesterol (mg/dl)		123.9 (118.6- 129.2)	106.7 (101.4- 112.1)	<0.001
Creatinine (umol/L)		61.8 (58.8- 64.8)	57.1 (54.1 - 60.2)	0.035
Fasting insulin (pmol/L)		10.2 (9.54 - 10.9)	6.9 (6.50 - 7.48)	<0.001
HOMA-IR		3.43 (3.15- 3.72)	1.38 (1.37-1.49)	<0.001
HOMA-β (%)		58.2(50.9 – 66.6)	159.2 (138.6- 182.3)	<0.001

Data presented as geometric means with a 95% confidence interval of the mean, and as frequency (percentage). P-value significant at $\leq$ 0.05.

Statistical Analysis

The Hardy-Weinberg equilibrium (HWE) analysis was conducted using the Chi-square test in the SPSS program (SPSS Version 26; SPSS Inc., Chicago, USA), by using observed Genotype frequencies derived from study data and anticipated genotype frequencies computed using the Hardy-Weinberg equation. Demographic and biochemical characteristics were evaluated using Analysis of Covariance (ANCOVA), with adjustments made for age and BMI. The associations of the KCNQ1 SNP with T2DM were assessed using logistic regression analysis in recessive, dominant, and additive models, while controlling for age, gender, and BMI as factors.

RESULTS

Patients with T2D exhibited elevated BMI, age, blood glucose, insulin levels, insulin resistance, triglycerides, LDL, creatinine, and total cholesterol compared to normal participants; nevertheless, HOMA-β was diminished in T2D patients relative to normal people (Table 1).

Based on the table 2, SNP of ***KCNQ1***: rs2237892does not differ from Hardy-Weinberg Equilibrium (*P*-value = 0.644 in non-diabetic subjects).

Correlation of KCNQ1 SNP with T2DM

The Hardy-Weinberg equilibrium was not deviated from by the SNP of the study's control group. The frequency of risk allele rs2237892 (C) was 0.89 in healthy people and 0.92 in diabetes. T2D was not associated with the additive genetic model (OR = 1.489, *P* = 0.15 and OR = 0.335, *P* = 0.153, respectively), but it was associated with the recessive genetic model of rs2237892 in Yemeni individuals (OR = 2.698, P = 0.01).

The recessive model; odds ratio (CC vs (CT + TT)).Dominant model; odds ratio ((CC + CT) vs TT).The additive model; odds ratio (CC vs CT vs TT). The additive model was re-coded for 2 within genotype CC, 1 within genotype CT, and 0 within genotype TT. The model was then modified to account for body mass index, sex, and age. The findings are displayed as a frequency, P-value, and the corresponding odds ratio.

The Binary logistic regression model, after adjusting gen-

Table 2. Analysis of Hardy-Weinberg Equilibrium for the KCNQ1 SNP genotype among Yemeni individuals

***KCNQ1*SNP**	Location of SNP on Chromosome 11 *	***HWE*** *P*-Value		Exon
		Non-diabetic	T2D	
rs2237892	Chr 11:2818521	**0.644**	<0.001	16

Table 3. Correlation of KCNQ1 rs2237892 with T2DM evaluated by additive, recessive, and dominant models

SNP	Group	Risk allele frequency	Genotype *n* (frequency)	Recessive model		dominant model		additive model	
				$OR_{(95\% CI)}$	*P*-value	$OR_{(95\% CI)}$	*P*-value	$OR_{(95\% CI)}$	*P*-value
The Binary logistic regression model, after adjusting gender, age, and body mass index (BMI),									
rs:2237892	Normal N (150)	C	CC CT TT	2.698 (1.270-5.73)	**0.01**	0.335 (0.075-1.499)	**0.153**	1.489 (0.857-2.58)	**0.15**
		133.5 (0.89)	120 (0.80) 27 (0.18) 3 (0.02)						
	Diabetic N (150)	137.5 (0.92)	133 (0.89) 9 (0.06) 8 (0.05)						

The recessive model; odds ratio (CC vs (CT + TT)). Dominant model; odds ratio ((CC + CT) vs TT). The additive model; odds ratio (CC vs CT vs TT). The additive model was re-coded for 2 within genotype CC, 1 within genotype CT, and 0 within genotype TT. The model was then modified to account for body mass index, sex, and age. The findings are displayed as a frequency, P-value, and the corresponding odds ratio.

der, age, and body mass index (BMI).

DISCUSSION.

Over the past 20 years, genome-wide association studies (GWAS) and case-control studies have revealed over 700 inherited risk factors for type 2 diabetes, predominantly in East Asians and Europeans [18].The rs2237892 polymorphism in KCNQ1 was examined concerning T2D. The KCNQ1 polymorphism rs2237892 was selected for the current investigation after conducting candidate gene investigations.Initially, genome-wide association studies and replication studies were conducted across various ethnic groups. The putative correlation between the KCNQ1 rs2237892 (C/T) gene polymorphism and patients with type 2 diabetes mellitus (T2DM) was investigated in this study. According to this study, the mean age of diabetic patients was substantially higher than that of non-diabetic people,53.57 (52.09-55.03) for diabetics and 49.96 (48.49-51.42) for non-diabetics. Other research has reported comparable results [19].Biochemical tests showed that diabetic individuals exhibited significantly increased levels of LDL-C, triglycerides, and total cholesterol compared to controls ($p< 0.05$). Lipid abnormalities associated with diabetes mellitus are believed to be caused by insulin-resistant fat cells, which produce more free fatty acids. Apolipoprotein B and very low-density lipoprotein C synthesis are enhanced when glycogen stores are sufficient because the liver receives a greater quantity of free fatty acids. Synthesis of TG results from this procedure. The production of VLDL-C by the liver increases when insulin's efficacy in preventing the release of free fatty acids decreases. Due to an increase in VLDL-C particles and plasma TG levels, HDL-C levels decrease as the concentration of small, dense LDL-C increases [20]. This outcome was comparable to a study conducted by Ahmed Tijani Bawah and colleagues[21].The most common cause of diabetes is excess body fat. The relation between BMI and T2DM is dose-response, Hartemink et al. meta-analyzed. Even after accounting for research heterogeneity, diabetes risk increased by 18% (95% CI 1.16% to 1.20%) for every kg/m2 rise in BMI [22].The findings regarding body mass index (BMI) were comparable with previous studies conducted on the Yemeni population and showed a highly statistically significant difference ($p < 0.001$) [23]. Their findings suggested that persons with T2D in Yemen often exhibited elevated BMI.

CORRELATION OF KCNQ1 RS22337892 WITH T2DM

Many genes interact with environmental and genetic factors to cause hyperglycemia. As a result, researchers have used various approaches to discover the genes associated with T2DM. However, studies conducted

across different geographic regions and among diverse ethnic populations yielded a range of outcomes worldwide. Multiple investigations have shown that SNPs in KCNQ1 rs2237892 correlate with type 2 diabetes[24, 25].The main SNPs for T2D risk in healthy people affect insulin synthesis, which leads to β-cell malfunction, instead of insulin action, which results in insulin resistance. This study shows that β-cell bulk or function abnormalities, or both, are important predisposing factors for T2D [26, 27].According to the study's findings, the T2D group's KCNQ1 genotyping distribution frequency for SNP rs2237892 was 89% CC, while the non-diabetic group's was 80%. 6% of the T2D group and 18% of the non-diabetic group had the CT (heterozygous) genotype. 5% of the T2D group and 2 % of the non-diabetic group had the TT genotype. 89% of the control group and 92% of the T2D group carried the risk allele (C). This study discovered a strong correlation between type 2 diabetes mellitus and the alternative KCNQ1 variant, rs2237892. This result is consistent with research on Thai populations and Chinese populations in Shanghai and Hong Kong [28, 29] and Northwestern China [30], and throughout the Korean populace [31].After controlling for gender, age, and body mass index (BMI), the correlation between the KCNQ1 mutation and type 2 diabetes was much stronger. The logistic regression model showed that the odds ratio for the recessive model was after accounting for age, gender, and BMI(OR=2.69, P =0.01). However, there was no correlation between T2D and either the dominant or additive genetic models of rs2237892. This study disagreed with earlier research on the Saudi populace [32] and among Arabs in Tunisia [33].The increased risk of type 2 diabetes linked to the KCNQ1 gene is most likely due to decreased insulin synthesis[34].Potassium channels comprise the regulatory beta subunit ISK, encoded by the KCNE1 gene, and the pore-forming alpha subunit KvLQT1, expressed by the KCNQ1 gene[35].Changes in single-nucleotide polymorphisms (SNPs) in KCNQ1 can affect how the potassium channel works, leading to lower insulin secretion and, as a result, T2D [36].

CONCLUSION

This study showed a correlation between type 2 diabetes in Yemeni individuals and the recessive genetic model of the KCNQ1 SNP rs2237892.

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