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Effect of rs10440833 polymorphism in the *CDKAL1* gene on insulin secretion in type 2 diabetes patients

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ABSTRACT

In the present generation, type 2 diabetes mellitus (T2DM) has become a common disease with the same trend in the Saudi Arabia due to many factors. Apart from environmental factors, genetic factors are also playing the major role. In this context, this study has design to screen a polymorphism related to T2DM and which was not studied yet in the Saudi Arabia and this study was designed by selecting rs10440833 polymorphism in *CDKAL1* gene. The aim of this study was to execute the genetic association with rs1044883 polymorphism in the *CDKAL1* gene in Saudi patients diseased with T2DM. In this study, 60 T2DM patients and 60 controls were selected and genotyping was carried with PCR-RFLP analysis using ACIL restriction enzyme. The obtained data was calculated with SPSS software and the tables were generated. The current study results confirmed, that some of the clinical parameters significantly differ between T2DM cases and control subejcts ($p < 0.05$). Genotype and allele frequencies showed negative association ($p > 0.05$). However, both regression and ANOVA analysis was also showed negative association ($p > 0.05$). In conclusion, the rs10440833 polymorphism is not associated in the Saudi Arabian T2DM patients and this polymorphism has no role.

1. Introduction

Diabetes is defined as chronic and metabolic disorder in which carbohydrate, lipid and protein metabolism results towards the combined combination of insulin secretion and insulin action (武玉莲, 李素萍, 张泽, 袁超燕., 2015). The estimation of diagnosed diabetes subjects was recorded for 536.6 million till 2021 worldwide (Al Mansour, 2020). The prevalence of diabetes in the Saudi population was found to be 31.6 % in the general population and 14.1 % in the working population. However, when it comes towards the distribution in genders, 34.6 % of diabetes was found in males and 27.6 % in females. The prevalence of T2DM in Oman, Bahrain and Kuwait was found to be 16.1 %, 25.7 % and 21 % respectively. However, Saudi Arabia has the highest prevalence of diabetes when compared with other Gulf Cooperation Council nations (Al-Daghri et al., 2014). Type 2 Diabetes Mellitus (T2DM) is described this disorder as reduced insulin secretion from pancreas or elevated insulin resistance. From 2013 to 2035, the International Diabetes Federation predicts that the number of people with type 2 diabetes might rise from 382 to 592 million (Al-Daghri et al., 2014). Obesity can be considered as one of the major risk factors for T2DM worldwide, same for the Saudi population. Based on WHO reports, the prevalence of overweight and obesity in the Saudi Arabia is 68.2 % and 33.7 % (Alharbi et al., 2021). The comorbidities of T2DM includes liver, neurological and cardiovascular diseases and the development of T2DM is due to genetic and environmental factors (Alharbi et al., 2013). The role of genes in T2DM has previously been explored, and large-scale genotyping using the Metabochip revealed that several loci enhance susceptibility to T2DM (Ali Khan et al., 2023). Genome-wide association studies have identified many genetic polymorphisms and cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1 (CDKAL1) was one of the gene linked to T2DM. The *CDKAL1* gene is present on chromosome region of 6p22.3 and is expressed in human pancreatic islet and skeletal muscle (Alshammary, 2023). It spans about 37 kb which encodes 579 amino acids and this gene encode tRNA decoration enzyme which is describes as methyl transferase enzyme (Alshammary et al., 2023). The rs10440833 polymorphism was commonly associated in T2DM. The aim of this study was to investigate the genetic role of rs10440833 polymorphism in the Saudi population confirmed with T2DM.

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2. Materials and methods

2.1. Recruitment of diabetes subejcts

Ethical approval was received for this study from Instructional Review Board, College of Medicine at King Saud University (KSU). All the patients involved in this study has approved the consent form with their signatures. This study was carried out using Helsinki Declaration. In this case-control study, 60 T2DM and 60 controls were recruited based on the previously published studies (武玉莲, 李素萍, 张泽, 袁超燕., 2015). The inclusion criteria for T2DM in based on fasting blood sugar (FBS) should not exceed 7.0 mmol/L. The normal glucose values for control group were < 7.0 mmol/L. The exclusion criteria are the T2DM patients without diagnosing diabetes and with the normal glucose values. The inclusion criteria for control subjects are based on normal glucose levels and individuals are not diagnosed with diabetes previously. The exclusion criteria for control diabetes are with elevated glucose values. The collection of T2DM and controls was described in the documented study (Alshammary and Khan, 2021). The estimation of sample size was also selected from the previously published studied in the Saudi population (武玉莲, 李素萍, 张泽, 袁超燕., 2015).

2.2. Clinical data

The clinical data of recruited individuals (SBP, DBP and BMI) (Alshammary et al., 2023); (Alsulami et al., 2023).

2.3. Blood and analysis

In this study, 0.5 ml of aliquoted EDTA blood was collected from 120 subjects.

2.4. Biochemical analysis

The biochemical parameter was collected within the hospital premises. The serum values were fasting blood sugar (FBS) and lipid profile parameters were collected. Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC) tests will be in lipid profile. Based on previous study analysis, the tests was performed (Ching et al., 2002).

2.5. Molecular analysis

Genomic DNA was isolated using Norgen DNA isolation kit from blood following manufacturer protocol (Cat# 51104, Applied Biosystems, Hilden, Germany). DNA was measured with the NanoDrop spectrophotometer (Thermoscientifics, Madison, WI, USA). DNA was stored at −80 °C until further use. Genotyping (Applied Biosystems, Model# 9902, Singapore) was performed with polymerase chain reaction (PCR) for rs10440833 using F: AATTAATATTCCCCCCTGTATTTTAGT and R: GCTCATTGCTACATAATAATAACTGTAGAT. The amplification was with 50 µl reaction using Qiagen master mix (Lot# 1151234588, Hilden, Germany), 10pmoles of primers, DNA templates and final volume was make-up with double distilled water. The initial denaturation was run on 95 °C for 5mins, denaturation at 95 °C for 30 s, 60 °C for annealing temperature, 72 °C for 45 s was the extension and the final extension took place at 72 °C for 5mins. The PCR was completed after 35cycles and hold at 4 °C. PCR products were run on 2 % agarose gel and 158 bp was obtained. Digestion was performed with *ACIL* restriction enzyme (CAT# R0551L, New England Biolabs, UK) and PCR products were digested at 37 °C for 18 h and A allele confirms 158 bp, while C allele confirms 122 and 36 bp after running the RFLP products on 2 % agarose gel (Lonza, CAT# 50004, NY, USA).

2.6. Statistical analysis

The statistical analysis was performed using SPSS software (Version 26.0, Chicago, IL, USA). Both categorical and numerical variables was tested using chi-square and student t-tests. Hardy-Weinberg Equilibrium (HWE) analysis was conducted to evaluate the difference between the genotypes present in T2DM cases and controls. Genotyping and allele frequencies was calculated using odds ratios (ORs), 95 % confidence intervals (95 %CIs) and p values. Logistic regression was studied between rs10440833 polymorphism and T2DM variables. One-Way analysis of variance (ANOVA) was studied between three different genotypes and T2DM variables (Khan et al., 2019). P is considered as less than 0.05 towards the statistical significance ($p \leq 0.05$).

3. Results

3.1. Clinical features

Both clinical and demographic features of T2DM cases and control subjects were showed in Table 1. The controls data was used as a reference for comparing data present in the T2DM cases. A strong significance difference was present in age, SBP, DBP, FBS, TC and TG ($p < 0.05$) when compared between T2DM cases and controls. However, gender, weight, height, BMI, HDLC and LDLC was not associated ($p > 0.05$). The family history of T2DM was having 46.7 % and control group were 40 % which was also non-significant ($p > 0.05$).

3.2. Genotyping analysis

The HWE analysis was found to be consistent with control subjects as well as T2DM cases ($p > 0.05$). The rs10440833 polymorphism was genotyped in 120 subjects (60 individuals for T2DM and control each). The call-rate for genotype loci of rs10440833 was determined to be more than 90 %, indicating that it adds to the dependability of the findings of this study. The AA, AC and CC genotypes of T2DM cases and control subjects were found to be 90 %, 8.3 %, 1.7 % and 95 %, 3.3 %, 1.7 % respectively. Genotype frequencies (AC vs AA: OR-2.63 (95 %CI:0.49–14.18); $p = 0.24$ and CC vs AA: OR-1.05 (95 %CI: 0.06–17.3); $p = 0.96$), combined genotype models (AC + CC vs AA: OR-2.11 (95 %CI: 0.50–8.86); $p = 0.30$; AA + CC vs AA: OR-0.37 (95 %CI: 0.07–2.03); $p = 0.24$ and AC + AA vs CC: OR-1.00 (95 %CI: 0.06–16.36); $p = 0.24$) were calculated between T2DM and control subejcts. The allele frequencies between A and C alleles in T2DM cases and controls was found to be 94.2 %, 5.8 % and 96.7 %, 3.3 % respectively (C Vs A: OR-1.79 (95 %CI: 0.51–6.30); $p = 0.35$). There was no genetic association either in genotypes or allele frequencies present in T2DM cases and control subjects (Table 2).

Table 1
Clinical characteristics features present in T2DM and control groups.

Characteristics	T2DM (n = 60)	Controls (n = 60)	P value
Age (Years)	54.75 ± 8.91	45.07 ± 6.91	<0.001
Gender (Male: Female)	51 (85 %):9 (15 %)	34 (56.7 %):26 (43.3 %)	0.68
Weight (kgs)	77.71 ± 13.89	77.01 ± 14.65	0.78
Height (cms)	162.64 ± 8.53	161.37 ± 8.63	0.41
BMI (kg/m^2)	29.59 ± 7.09	29.50 ± 5.72	0.93
SBP (mmHg)	124.78 ± 10.81	113.82 ± 9.12	<0.0001
DBP (mmHg)	80.97 ± 6.90	76.25 ± 6.93	0.002
FBS (mmol/L)	12.93 ± 5.18	5.08 ± 0.74	<0.0001
TC (mmol/L)	2.05 ± 1.19	1.60 ± 0.88	0.02
TG (mmol/L)	5.43 ± 1.22	4.96 ± 1.00	0.02
HDLC (mmol/L)	0.69 ± 0.23	0.65 ± 0.27	0.38
LDLC (mmol/L)	3.84 ± 0.99	3.55 ± 0.83	0.08
Family History	28 (46.7 %)	24 (40 %)	0.87

BMI= Body Mass Index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, FBS= Fasting Blood Sugar, TC= Total Cholesterol, TG= Triglycerides, HDLC= High Density Lipoprotein Cholesterol and LDLC= Low Density Lipoprotein Cholesterol.

Table 2
Genotype and allele frequency studies between rs10440833 polymorphism in T2DM and controls.

Genotypes and Alleles	T2DM cases (n = 60)	Controls (n = 60)	OR (95 %CI)	P value
AA	54 (90 %)	57 (95 %)	**Reference**	**Reference**
AC	5 (8.3 %)	2 (3.3 %)	OR-2.63 (95 % CI:0.49–14.18)	p = 0.24
CC	1 (1.7 %)	1 (1.7 %)	OR-1.05 (95 %CI: 0.06–17.3)	p = 0.96
AC + CC vs AA	6 (10 %)	3 (05 %)	OR-2.11 (95 %CI: 0.50–8.86)	p = 0.30
AA + CC vs AC	55 (91.7 %)	58 (96.7 %)	OR-0.37 (95 %CI: 0.07–2.03)	p = 0.24
AC + AA vs CC	59 (98.3 %)	59 (98.3 %)	OR-1.00 (95 %CI: 0.06–16.36)	p = 0.24
A allele	113 (94.2 %)	116 (96.7 %)	**Reference**	**Reference**
C allele	7 (5.8 %)	4 (3.3 %)	OR-1.79 (95 %CI: 0.51–6.30)	p = 0.35

3.3. Linear regression model

The Table 3 of this study was calculated the linear regression model studied between rs10440883 polymorphism and T2DM parameters which includes age, weight, height, BMI, SBP, DBP, FBS, TG, TC, HDLC and LDLC parameters. Using SPSS software, all the parameters were measured and none of the genotypes showed the positive association towards this study. This means that no correlation was identified between the rs10440833 polymorphism and the T2DM characteristics used in this study.

3.4. ANOVA studies

ANOVA analysis (Table 4) was compared between AA, AC and CC genotypes present in rs10440833 polymorphism and T2DM parameters such as age, weight, height, BMI, SBP, DBP, FBS, TG, TC, HDLC and LDLC. None of the parameters was found to be associated between 3 genotypes and T2DM parameters ($p > 0.05$).

4. Discussion

The aim of this study was to examine the genetic association studies in T2DM patients and rs10440883 polymorphism in the Saudi Arabia. The current study results confirmed none of the genotype or allele frequencies were associated ($p > 0.05$) with studied SNP. Also, other genetic and statistical tests such as regression and ANOVA models also showed the negative association ($p > 0.05$). Only clinical parameters of analyzed groups showed the positive association between T2DM cases and control subjects with studied parameters such as age, SBP, DBP, FBG, TC and TG parameters ($p < 0.005$). Based on this study, it can be confirmed as rs10440833 polymorphism has no role in T2DM subjects in the Saudi Arabia. One of the major factors for negative association is may be due to the low sample size. However, similar polymorphism was studied in the Saudi population with obesity subejcts by Al-Daghri *et al* (Huang et al., 2023) studied and this study also showed the negative association (Erfanian et al., 2023). The study was conducted in 975 BMI, 825 pre-BMI and 423 subejcts with non-BMI controls. This large sample size study showed the negative association with 10440833 polymorphisms in the Saudi population. So, finally it can be concluded as rs10440883 polymorphism has no role when it was studied in large or small sample sizes. The cyclin-dependent kinase associated protein 1 (CDK5RAP1)-like 1 (CDKAL1) gene encodes a protein with similarity to CDK5RAP1. The serine/threonine protein kinase CDK5 assisted in the glucose-dependent regulation of insulin secretion. Glucotoxicity, β-cell dysfunction, and susceptibility to T2DM are all influenced by CDK5, which has a permissive role in each of these processes. CDKAL1 has a protein domain with CDK5RAP1, a CDK5 inhibitor that acts as a negative regulator of CDK5. The link between CDKAL1 and CDK5-mediated pathways is supported by the observation that CDKAL1 is expressed in human pancreatic β-cells. Multiple investigations have shown that CDKAL1 genetic variations are linked to impaired proinsulin conversion and insulin responsiveness to glucose stimulation. It follows that CDKAL1 is a crucial protein in the etiology of T2DM (Li et al., 2023; Li et al., 2013; Li et al., 2023; Naeem, 2015; Ng et al., 2014). The main limitation of this study includes low sample size and only 10440833 polymorphism was studied. The major strength of this study was to conduct the case-control study i.e., between T2DM cases and control subjects in the Saudi population.

The rs10440833 polymorphism was studied globally in T2DM subejcts. The diverse association was present in the T2DM subejcts and rs10440833 polymorphism (Pascoe et al., 2007; Safarpour et al., 2015; Steinthorsdottir et al., 2007; Thompson et al., 2018; Tian et al., 2019). The rs10440833 polymorphism was studied in other human diseases apart from T2DM (Alshammary, 2023; Huang et al., 2023; Ubeda et al., 2006). The *meta*-analysis studies were also studied with rs10440833 polymorphism (Verma et al., 2021) confirmed stronger effect in European population in comparison towards African Americans (Verma et al., 2021).

The prevalence of diabetes is increasing in Saudi Arabia. One of the community-based study was conducted to screen the accurate prevalence of diabetes and the questionnaire-based study, it was documented as 23.7 % of subjects were confirmed: from 16.9 k participants finally 4 k subjects have confirmed as diabetics. But it's also having a significant impact in urban areas, especially for male subjects (Youkhana et al., 2018). The importance of family history in the Saudi population is also

Table 3
Linear regression model compared between rs10440833 polymorphism and T2DM parameters.

Dependent variables	R-value	Adjusted R square	F	p value
Age (Years)	0.009	0.000	0.005	0.94
Weight (kgs)	0.141	0.020	1.172	0.28
Height (cms)	0.134	0.001	1.057	0.31
BMI (kg/m^2)	0.038	−0.016	0.084	0.77
SBP (mmHg)	0.035	−0.016	0.071	0.79
DBP (mmHg)	0.172	0.013	1.773	0.18
FBS (mmol/L)	0.030	−0.016	0.053	0.82
TG (mmol/L)	0.144	0.004	1.224	0.27
TC (mmol/L)	0.065	−0.013	0.244	0.62
HDLC (mmol/L)	0.142	0.003	1.190	0.28
LDLC (mmol/L)	0.047	−0.015	0.130	0.72

BMI= Body Mass Index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, FBS= Fasting Blood Sugar, TC= Total Cholesterol, TG= Triglycerides, HDLC= High Density Lipoprotein Cholesterol and LDLC= Low Density Lipoprotein Cholesterol.

Table 4
ANOVA studies compared between genotypes of rs10440833 polymorphism and T2DM parameters.

Dependent variables	AA (n = 54)	AC (n = 05)	CC (n = 01)	P value
Age (Years)	54.7 ± 9.1	55.0 ± 7.9	55.0 ± 1.00	0.98
Weight (kgs)	77.0 ± 14.1	84.1 ± 12.2	83.0 ± 1.00	0.51
Height (cms)	162.3 ± 8.6	165.0 ± 7.9	160.0 ± 1.00	0.75
BMI (kg/m^2)	29.5 ± 7.3	31.1 ± 5.8	28.7 ± 1.00	0.88
SBP (mmHg)	125.3 ± 11.0	120.0 ± 8.2	118.0 ± 1.00	0.47
DBP (mmHg)	81.5 ± 6.6	76.0 ± 8.9	80.0 ± 1.00	0.22
FBS (mmol/L)	12.9 ± 5.5	13.2 ± 0.9	14.6 ± 1.00	0.94
TG (mmol/L)	1.6 ± 0.9	1.4 ± 0.5	0.73 ± 1.00	0.56
TC (mmol/L)	5.0 ± 1.0	5.1 ± 0.9	3.79 ± 1.00	0.42
HDLC (mmol/L)	0.7 ± 0.2	0.8 ± 0.2	0.87 ± 1.00	0.41
LDLC (mmol/L)	3.5 ± 0.8	3.8 ± 0.7	2.58 ± 1.00	0.36

BMI= Body Mass Index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, FBS= Fasting Blood Sugar, TC= Total Cholesterol, TG= Triglycerides, HDLC= High Density Lipoprotein Cholesterol and LDLC= Low Density Lipoprotein Cholesterol.

playing a major role towards the replication of the disease in the future generation. However, the population in Saudi Arabia is around 28 million in the Saudi families and the progress of the disease is expanding rapidly in the future generations.

Missing of validation with DNA sequencing analysis was one of the limitations of this study (Zeggini et al., 2007). Still DNA sequencing is considered as the gold standards method to identify the specific nucleotide in the DNA sequencing analysis.

5. Conclusion

In conclusion, this study confirms as rs10440833 polymorphism has no role in the T2DM patients of the Saudi Arabia. Similar lack of significance of rs10440833 polymorphism has no role in obesity patients of Saudi Arabia (Huang et al., 2023). Future studied will be advising to study with large sample size.

Declaration of competing interest

The author declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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