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Association of serine racemase gene polymorphism with type 2 diabetes mellitus

May Salem Al-Nbaheen *

Public Health Department, College of Health Sciences, Saudi Electronic University, Riyadh, Saudi Arabia

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and β-cell dysfunction, with a significant global impact. Genome-wide association studies (GWAS) have identified several genetic polymorphisms linked to T2DM, including the rs391300 polymorphism in the SRR gene. This study aimed to evaluate the association between the rs391300 polymorphism and T2DM in the Saudi population. A total of 160 participants, comprising 80 T2DM patients and 80 healthy controls, were genotyped using quantitative PCR with VIC and FAM probes. The results revealed a significant association between T2DM and age, body mass index (BMI), glucose levels, and cholesterol levels. Genotype and allele frequency analysis demonstrated that the rs391300 polymorphism was linked to a higher risk of T2DM (GA vs. AA: OR = 4.75, 95% CI: 1.52–14.94, p = 0.04; A vs. G: OR = 4.33, 95% CI: 1.42–13.27, p = 0.005). Additionally, ANOVA analysis indicated a significant association with weight and BMI (p = 0.01). This study provides evidence of a positive association between the rs391300 polymorphism in the SRR gene and T2DM in the Saudi population.

1. Introduction

The World Health Organization (WHO) classifies diabetes as a group of metabolic disorders characterized by persistent hyperglycemia and changes in carbohydrate, lipid, and protein metabolism due to deficiencies in insulin production, insulin action, or both (Khan, 2021). The International Diabetes Federation estimates the number of people with diabetes will increase from 537 million in 2021 to 783 million in 2045 (Alharbi et al., 2021a). Type 2 diabetes mellitus (T2DM) is a global health issue that places a significant socioeconomic burden on the healthcare system (Naseri et al., 2023).

More than two-thirds of people with T2DM are overweight or obese at the time of diagnosis, making obesity a major risk factor. The co-morbidities, including non-alcoholic fatty liver, cardiovascular disease, and kidney disease, have a significant role in the early mortality rates linked with both obesity and T2DM (Bailey et al., 2023). Multiple disorders are linked to single nucleotide polymorphisms (SNPs), and several have been studied in depth to shed light on the molecular causes of T2DM, such as β-cell dysfunction, insulin resistance, and impairment of incretin signaling (Alshammary et al., 2023a). Specific challenges arise in T2DM subjects due to the continual decline in exocrine pancreatic β-cell secretion of sufficient insulin. Chronic low-grade and asymptomatic inflammation are well-established to play a pivotal role in the development of T2DM. The HbA1c level is the single most important indicator of future risk of diabetes (Wang et al., 2023).

T2DM is primarily a hereditary illness characterized by insulin insufficiency as a consequence of inadequate secretion of insulin by β-cells in the pancreas and insulin resistance as a result of incorrect response to insulin by the insulin-sensitive tissues. The inability of target cells, such as adipose tissue, liver, and muscle, to respond to insulin leads to reduced glucose uptake and utilization, which is the definition of Insulin resistance (Alzahrani et al., 2023). Recent studies have found that being over the age of 45, having a body mass index (BMI) over 25kg/m2, having a family history of DM, having abdominal obesity, coming from a lower socioeconomic background, and eating fewer fruits and vegetables than recommended significantly increased the chance of developing T2DM. There are about 46 million

* Corresponding Author.
Email Address: malnbaheen@seu.edu.sa
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Corresponding author's ORCID profile:
https://orcid.org/0000-0003-4354-2726

persons with T2DM in the Middle East (Alwadeai and Alhammad, 2023). Currently, the prevalence of T2DM in Saudi Arabia is 32.8%, and it is projected to grow to 35.4% in 2020 and 45.8% in 2030 (Alzaheb and Altemani, 2020).

Genetic factors play an important role along with environmental factors in T2DM disease (Khan et al., 2019). T2DM is considered a polygenic disease, meaning it is influenced by multiple genes, each contributing partially and collectively to its development (Tsai et al., 2010). The modifiable risk factors for T2DM include dyslipidemia, obesity, oxidative stress, smoking, exercise, and alcohol intake, and non-modifiable factors including age, sex, a positive family history, and genetic susceptibility (El-Lebedy et al., 2016). Genome-wide association studies (GWAS) examine the frequency of alleles of genetic polymorphisms in populations with similar ancestry but different traits in an effort to uncover relationships between genotypes and phenotypes. Single nucleotide polymorphisms (SNPs) are the most widely investigated genetic variants in GWAS. However, copy-number variants and sequence differences in the human genome can also be considered (Uffelmann et al., 2021). GWAS have confirmed more than 40 SNPs in T2DM disease (Khan et al., 2015), and Tsai et al.'s (2010) studies have identified rs391300 polymorphism in Serine racemase (SRR) gene through GWAS studies carried out in the Chinese population (Tsai et al., 2010). There is significant evidence linking the area containing the polymorphism rs391300 on chromosome 17p13.3 to T2DM. Serine racemase (SRR) is an enzyme encoded by the SRR gene that converts L-serine to D-serine. It plays a role in regulating glucose balance in pancreatic β-cells, and the glutamate signaling pathway also supports the release of glucagon and insulin in pancreatic islets (Dong et al., 2011).

Currently, the prevalence of no communicable diseases (NCDs) is increasing in the Saudi population, including T2DM, and the rs391300 polymorphism has not been examined. In this present study, the investigation was performed between rs391300 polymorphism in T2DM patients in the Saudi population.

2. Methodology

2.1. Study participants

This study included 160 participants, consisting of 80 T2DM cases and 80 control subjects. It was conducted at King Saud University (KSU) Hospital in Saudi Arabia. Participants were selected from Riyadh due to its large population and the high prevalence of diabetes, particularly T2DM. The sample size for each group was calculated using the formula provided by Charan and Biswas (2013). T2DM cases were enrolled based on the American Diabetes Association (ADA) criteria as described in prior research (Al-Nbaheen, 2022). Control subjects were those with normal glucose levels, defined as fasting blood sugar (FBS) less than 7.2 mmol/L, along with normal post-prandial blood sugar (PPBS) and glycated hemoglobin (HbA1c) levels at the time of enrollment. Sample collection was carried out at KSU between 2012 and 2014.

2.2. Ethical and anthropometric measurement details

Ethical approval for the study was obtained from the hospital, and all participants signed informed consent forms. The study followed the Declaration of Helsinki guidelines (Shephard, 1976). Anthropometric measurements, including age, weight, height, and BMI, were recorded (Alshammary and Khan, 2021). BMI was categorized into three groups: normal, overweight, and obese. Both male and female participants provided 5 mL of venous blood, which was collected by nurses at KSU. For HbA1c testing and DNA extraction, 2 mL of blood was placed into a vacutainer tube containing ethylenediaminetetraacetic acid (EDTA). The remaining 3 mL of blood was collected in a coagulant vacutainer tube for FBS, PPBS, and lipid profile analysis.

2.3. Laboratory analysis

A total of 1 mL of fasting blood and 2 mL of non-fasting blood were collected in separate tubes. The fasting blood sample was drawn at least 9 hours before the start of fasting, and the non-fasting blood sample was collected during the post-prandial period (PPBS). These samples were used for lipid profile analysis, including measurements of high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG). Additionally, HbA1c analysis was conducted using the EDTA blood sample. The procedures followed were based on a previous study (Al-Nbaheen, 2022).

2.4. Molecular laboratory analysis

DNA isolation was conducted following the protocol described in a previous study (Al-Nbaheen, 2022), using EDTA blood and a Qiagen DNA isolation kit. The DNA quality was standardized to a concentration of 10 ng/µL using a NanoDrop spectrophotometer and stored in a freezer. For this study, the TaqMan genotyping method was employed to screen the rs391300 (C_11954783_10) polymorphism, using VIC to identify the G allele and FAM for the A allele. Genotyping was performed with a 25 µL reaction volume comprising TaqMan master mix, purified water, VIC/FAM probes, and DNA templates, using the ABI 7500 RT-PCR machine at an annealing temperature of 62°C. To ensure quality control, 15% of the samples were re-genotyped, and all results were consistent with the initial analysis. The genotyping procedure followed the protocol established in prior research (Alharbi et al., 2021b; Malkki and Petersdorf, 2012).

2.5. Statistical analysis

Data from T2DM cases and controls were analyzed using SPSS software (Version 21.0). The basic characteristics of the two groups were compared using Student's t-tests. Hardy-Weinberg Equilibrium (HWE) was assessed using chi-square tests. Genotype and allele frequencies were analyzed using odds ratios (ORs), 95% confidence intervals (95% CIs), and p-values. ANOVA was used to evaluate the association between T2DM patient characteristics and the rs391300 polymorphism. A p-value of less than 0.05 ($p \leq 0.05$) was considered statistically significant (Alshammar et al., 2023b).

3. Results

3.1. Studied characteristics

Table 1 in this study compares the two groups (T2DM cases and controls), which were matched by age and had an equal number of males and females. The study analyzed BMI, FBS, PPBS, HbA1c, HDLC, LDLC, TC, and TG values in both groups. A Student's t-test revealed that age, weight, BMI, FBS, PPBS, HbA1c, HDLC, and LDLC levels were significantly higher in the T2DM group, indicating an association with the condition. However, gender, TC, and TG levels showed no significant association.

Table 1: Basic characteristics of T2DM patients and controls tested with student t-tests analysis

T2DM details	T2DM (n=80)	Controls (n=80)	P-value
Age	59.01±5.85	54.12±5.14	<0.0001
Men	57 (71.25%)	57 (71.25%)	
Women	23 (28.75%)	23 (28.75%)	1.00
Height	159.64±8.39	158.41±8.13	0.34
Weight	74.34±11.32	69.16±10.38	0.002
BMI	29.24±4.46	27.61±4.15	0.01
FBS	6.11±2.29	3.87±1.32	<0.0001
PPBS	9.55±18.49	5.42±11.07	<0.0001
HbA1c	7.87±0.77	5.32±0.49	<0.0001
HDLC	0.66±0.25	0.56±0.23	0.009
LDLC	3.73±0.96	2.78±0.78	<0.0001
TC	4.92±1.33	4.63±1.24	0.15
TG	1.65±0.72	1.49±0.68	0.16

BMI: Body mass index; FBS: Fasting blood sugar; PPBS: Post-prandial blood sugar; HbA1c: Glycated hemoglobin; HDLC: High-density lipoprotein cholesterol; LDLC: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides

3.2. HWE-analysis for rs391300 polymorphism

HWE analysis was conducted for both T2DM cases and control subjects. The genotype frequencies for GG and GA genotypes were 80% and 20% in T2DM cases and 95% and 5% in controls, respectively. The AA genotype was absent in both groups. HWE analysis showed consistency in the control group ($\chi^2 = 0.05$, $p = 0.81$) and in the T2DM group for the rs391300 polymorphism ($\chi^2 = 0.98$, $p = 0.32$). The detailed results are presented in Table 2.

3.3. SRR rs391300 polymorphism and T2DM cases

Table 3 presents the genotype distribution analysis of the rs391300 polymorphism in T2DM cases and controls. The GG genotype and G allele were used as references for comparison. The GG genotype was observed in 80% of T2DM cases and 95% of controls, while the GA genotype was present in 20% of T2DM cases and 5% of controls. The AA genotype was absent in both groups. Statistical analysis revealed a strong association between the GA and GG genotypes, with an OR of 4.75 (95% CI: 1.52–14.94, $p = 0.04$). No association was found between the AA and GG genotypes (OR = 1.00, 95% CI: 0.01–5.10, $p = 0.99$) after the Yates correction.

Table 2: HWE analysis in rs391300 polymorphism in controls and T2DM subjects

rs391300	Controls	T2DM cases
Minor Allele	A	A
MAF	0.03	0.10
χ^2	0.05	0.98
P-value	0.81	0.32
GG genotype	95%	80%
GA genotype	05%	20%
AA genotype	00%	00%

MAF: Minor allele frequency; χ^2: Chi-square value; GG: Homozygous genotype (reference); GA: Heterozygous genotype; AA: Homozygous genotype for the minor allele

Table 3: Genotype and allele frequencies studied between T2DM cases and controls

	T2DM cases	Controls	ORs	95%CIs	P-value
Genotypes					
GG	64 (80%)	76 (95%)		Reference	
GA	16 (20%)	04 (5%)	4.75	1.52-14.94	0.04
AA	00 (0%)	00 (0%)	1.00	0.01-51.0	0.99
Alleles					
G	144 (90%)	156 (97.5%)		Reference	
A	16 (10%)	04 (2.5%)	4.33	1.42-13.27	0.005

GG: Homozygous genotype for the major allele; GA: Heterozygous genotype; AA: Homozygous genotype for the minor allele; ORs: Odds ratios; 95%CIs: 95% confidence intervals

3.4. Genetic association with rs391300 polymorphism

The genetic associations, such as dominant and co-dominant models, showed association (P=0.005), and the recessive model (P=0.99) showed no association with and without adding Yates correction. The details are presented in Table 4.

3.5. ANOVA analysis

ANOVA analysis was performed to examine the association between rs391300 genotypes and variables, including age, weight, BMI, FBS, PPBS, HbA1c, HDLC, LDLC, TC, and TG levels. The AA genotype was excluded as it was absent in T2DM cases. The analysis showed that weight and BMI were significantly associated with rs391300 genotypes ($p = 0.01$), while all other variables, including FBS, PPBS, and HbA1c levels, showed no significant association ($p > 0.05$). These findings suggest that the rs391300 polymorphism is not linked to key T2DM-related variables. Detailed results are presented in Table 5.

4. Discussion

The aim of this study was to evaluate the rs391300 polymorphism in the SRR gene and its association with T2DM in the Saudi population. To date, no studies have documented the relationship between the rs391300 polymorphism and T2DM in Saudi patients, making this the first study to do so. The heterozygous GA genotype was found in 20% of T2DM cases and 5% of controls, suggesting that the GA genotype carries a fourfold higher risk for T2DM. The odds ratio (OR) was found to be 4.3 times higher in T2DM patients for genotypes and 4.33 times higher for alleles. HWE was consistent in both the cases and controls.

Age, BMI, fasting blood sugar, and cholesterol levels were significantly higher in T2DM cases ($p < 0.05$). ANOVA analysis further showed a positive association with weight and BMI ($p = 0.01$).

Table 4: Genotype association using genetic models between T2DM cases and controls

	T2DM cases	Controls	ORs	95%CIs	P-value
Genetic models					
GA+AA vs GG	16 (20%)	04 (5%)	4.35	1.46-12.99	0.005
GA vs GG+AA	16 (20%)	04 (5%)	4.35	1.46-12.99	0.005
AA vs GA+GG	00 (00%)	00 (00%)	1.00	0.01-51.0	0.99

ORs: Odds ratios; 95%CIs: 95% confidence intervals

Table 5: ANOVA analysis studies between T2DM patients and rs391300 polymorphisms

T2DM details	GG (n=64)	GA (n=16)	AA (n=00)	P-value
Age	58.92±5.94	59.38±5.64	00.00±0.00	0.78
Weight	72.81±11.37	80.49±9.01	00.00±0.00	0.01
BMI	28.63±4.46	31.67±3.62	00.00±0.00	0.01
FBS	6.16±2.38	5.90±1.94	00.00±0.00	0.68
PPBS	9.94±20.66	7.99±2.11	00.00±0.00	0.71
HbA1c	7.84±0.78	7.95±0.74	00.00±0.00	0.61
HDLC	0.68±0.24	0.56±0.24	00.00±0.00	0.07
LDLC	3.78±1.01	3.52±0.71	00.00±0.00	0.33
TC	4.94±1.39	4.85±1.12	00.00±0.00	0.81
TG	1.63±0.73	1.74±0.73	00.00±0.00	0.59

GG: Homozygous genotype for the major allele; GA: Heterozygous genotype; AA: Homozygous genotype for the minor allele; BMI: Body mass index; FBS: Fasting blood sugar; PPBS: Post-prandial blood sugar; HbA1c: Glycated hemoglobin; HDLC: High-density lipoprotein cholesterol; LDLC: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides

The prevalence of DM and T2DM is increasing globally, primarily due to rising BMI and FBG levels, which are linked to unhealthy diets and reduced physical activity. T2DM prevalence increases proportionally with BMI. Additionally, population aging contributes to the higher prevalence of diabetes, as it is more common among older individuals (Khan et al., 2020). In Saudi Arabia, T2DM rates are rising alongside associated chronic diseases. The COVID-19 pandemic, recognized as an infectious disease, has also been linked to diabetes. Furthermore, obesity is highly prevalent within the Saudi population, exacerbating the issue.

SRR gene was identified by Tsai et al. (2010) when screening among the Chinese population under GWAS studies. There are only restricted studies were confirmed with T2DM and gestational diabetes mellitus (GDM). The functional role of the SRR gene was defined as the glutamate receptor co-agonist D-serine is produced when SRR metabolizes L-serine. Extracellular calcium concentration is increased in the brain during postsynaptic excitement because D-serine activates another receptor called N-methyl D-aspartate. Activated SRR D-serine proteins are often distributed in the central nervous system, cardiovascular system, kidneys, pancreas, and other organs. Glutamate signaling is regulated by D-serine conversion in pancreatic -cells, which regulates glucagon and insulin release. The risk of T2DM is raised because of the effects of this imbalance on glucagon and insulin production (Raza et al., 2020).

The current study results confirmed a positive association with genetic model, heterozygous, and allele frequencies in this study. This study was found to be in association with previous studies carried with rs391300 polymorphism (Dayeh et al., 2013; Girard et al., 2018; Shu et al., 2010; Sun et al., 2015; Tsai et al., 2010; Wang et al., 2011; Zhang et al., 2014) and other studies carried out in Chinese and

Japanese populations (Dong et al., 2011; Imamura et al., 2013). A meta-analysis study was carried out on T2DM and rs391300 polymorphism and confirmed the negative association (Zhang et al., 2014). Wang et al. (2011) studied rs391300 polymorphism in GDM women and confirmed the positive association. Raza et al. (2020) studied T2DM patients with rs1490763013 polymorphism in the SRR gene and confirmed the positive association (p=0.01).

In this study, 80 T2DM cases and 80 controls were selected, which can be the limitation of this study. The other limitation is to screen only one polymorphism. The strength of this study is to perform the real-time PCR analysis.

5. Conclusion

This study concludes that the GA genotype and A allele of the rs391300 polymorphism are associated with an increased risk of T2DM in the Saudi population. Additionally, some demographic factors were found to be associated with T2DM genotypes and related characteristics, as shown through ANOVA analysis. Further research with a larger population-based study is recommended for a more detailed investigation.

Compliance with ethical standards

Ethical considerations

This study was conducted in compliance with the ethical standards outlined in the Declaration of Helsinki. Ethical approval was obtained from the ethics committee at King Saud University Hospital, Riyadh, Saudi Arabia. Informed consent was obtained from all participants prior to their inclusion in the study, ensuring their understanding of the study's purpose, procedures, potential risks, and benefits. Participant confidentiality and anonymity were strictly maintained throughout the study.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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