

Original Research Article

EVALUATION OF KCNQ1 (RS2237892) GENE POLYMORPHISM AS A GENETIC DETERMINANT OF TYPE 2 DIABETES MELLITUS AMONG SOUTH INDIAN ADULTS

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder resulting from interactions between genetic, environmental, and lifestyle factors. Genetic variants affecting pancreatic β -cell function and insulin secretion may contribute to individual susceptibility to T2DM. The KCNQ1 gene has been identified as an important susceptibility gene for T2DM, and the rs2237892 single nucleotide polymorphism has been associated with diabetes risk in several ethnic populations. However, population-specific evidence from South India remains limited. The present study evaluated the association of KCNQ1 rs2237892 polymorphism with T2DM among South Indian adults. The aim is to analyze the KCNQ1 rs2237892 single nucleotide polymorphism among patients with T2DM and healthy controls and to evaluate its potential role as a genetic determinant of T2DM.

Materials and Methods: A hospital-based case-control study was conducted at K.A.P.V. Government Medical College and MGM Government Hospital, Tiruchirappalli, from September 2021 to August 2022. The study included 90 South Indian adults aged 40–60 years, comprising 45 patients with established T2DM and 45 healthy non-diabetic controls. Clinical and biochemical parameters were assessed, and genomic DNA was isolated from peripheral blood. The KCNQ1 rs2237892 region was amplified by polymerase chain reaction and genotyped using MspI restriction fragment length polymorphism analysis. Statistical analysis was performed using Student's t-test and Chi-square test, with logistic regression used to evaluate the association between the polymorphism and T2DM. A p-value <0.05 was considered statistically significant.

Results: The cases and controls were comparable with respect to age and BMI. Cases had significantly higher diastolic blood pressure, fasting blood sugar, and postprandial blood sugar than controls ($p < 0.001$). The diabetic group also demonstrated significantly higher total cholesterol and triglyceride levels and lower HDL cholesterol levels compared with controls ($p < 0.001$). A significant difference was observed in the distribution of KCNQ1 rs2237892 genotypes between cases and controls ($\chi^2 = 26.325$, $p < 0.0001$). The TT genotype was substantially more frequent among T2DM cases [27 (60.0%)] than controls [4 (8.9%)], whereas the CC and CT genotypes were more common among controls. At the allele level, the T allele was markedly more frequent among cases [66 (73.3%)] than controls [32 (35.6%)], while the C allele was more frequent among controls [58 (64.4%)] than cases [24 (26.7%)]. The difference in allele distribution was statistically highly significant ($\chi^2 = 25.893$, $p < 0.0001$). Logistic regression demonstrated an odds ratio of 4.98 (95% CI: 2.64–9.42; $p = 0.001$) for the T allele.

Conclusion: The present study demonstrates a significant association between the KCNQ1 rs2237892 polymorphism and type 2 diabetes mellitus among the South Indian adults studied. The T allele, particularly the TT genotype, was considerably more frequent among individuals with T2DM, suggesting that the T allele may represent a genetic susceptibility factor for diabetes in this population. The findings support a potential role of KCNQ1 rs2237892 in T2DM predisposition and provide population-specific evidence for its genetic contribution. However, the study included only 90 participants; therefore, larger population-based studies are required to validate these findings and establish the reproducibility of the observed association.

Keywords: KCNQ1; rs2237892; Type 2 diabetes mellitus; Genetic polymorphism; Single nucleotide polymorphism; T2DM susceptibility; South Indian adults.

INTRODUCTION

Non-communicable diseases are diseases which are chronic in nature and their etiology is mainly due to combination of various genetic, environmental, physiological and behavioral factors. They are generally termed as lifestyle diseases. Non-communicable diseases have become the most important health concern of world countries. As per WHO, NCD accounts for almost 74% of all deaths globally. This has an adverse impact on the National health policies, health system and adds to the economic burden of the country.^[1]

The important non-communicable diseases are coronary artery diseases, hypertension, diabetes mellitus, cancers and chronic respiratory diseases. Due to major lifestyle changes, like increased consumption of calorie-rich foods and decreased physical activity, and the ageing population, the incidence and prevalence of non-communicable diseases are on the increasing trend.

Diabetes Mellitus (DM) is a disease status due to inadequate control of blood glucose levels, resulting in hyperglycemia. The two main sub types of diabetes are Type I and Type II.

Type I is more common in children and adolescents and is characterized by deficient production of insulin due to auto immune destruction of insulin producing beta cells of the pancreas.^[2,3]

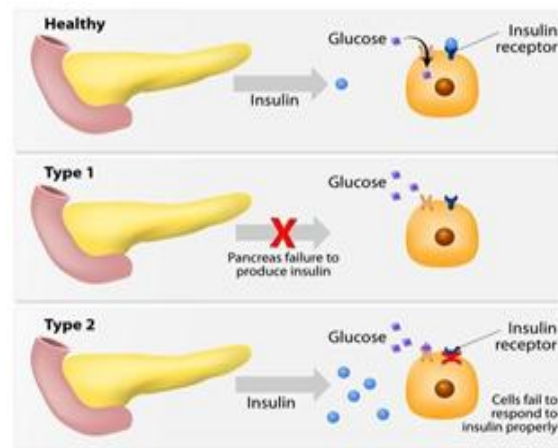
Type 2 diabetes is due to an imbalance between insulin production and action of insulin, characterized by resistance to insulin in tissues. Because of insulin resistance, there is initially an increase in production of insulin to maintain glucose homeostasis. With further passage of time, insulin production decreases, resulting in T2DM. Though the commonly affected age group is above 45 years, the incidence of the disease is seen increasing in younger age groups due to changing lifestyles.

Type 2 diabetes is multi-factorial and is one of the most common endocrine disorders, contributing to about 90% of total diabetes.^[2] Most of the type II diabetes patients are obese, with increased adipose tissue predominantly in the abdominal region, which further increases insulin resistance.^[4]

Derangement either in the production or action of insulin disturbs glucose homeostasis, which causes

hyperglycemia. Hyperglycemia is characterized by blood glucose levels above 125 mg/dL with fasting and 2 hours postprandial glucose above 180 mg/dL. Chronic hyperglycemia causes damage to kidneys, eyes, nervous system, vascular system and heart.

Diabetes Mellitus:



Type II diabetes has emerged into a major health issue which causes early morbidity and mortality, thus affecting the socioeconomic status of people. The burden of the disease is increasing globally.^[5,6] The world wide prevalence of diabetes was estimated as 9.3% (463 million people) in 2019. The Prevalence is expected to rise to (578 million) 10.3% by 2030 and (700 million) 10.9% by 2045. In India, the prevalence in 2019 was 77 million and is expected to increase to 134 million by 2045. The prevalence of diabetes is raising parallel to the increase in obesity.^[7,8]

Major complications of diabetes are life threatening and can be either Macro vascular (increasing the risk for cardiovascular diseases) or Micro vascular (neuropathy, nephropathy and retinopathy).

Diabetes is one of the most common non-communicable diseases. Diabetes mellitus is a chronic metabolic disorder associated with persistent hyperglycemia. Type I diabetes constitutes about 5% to 10% of total DM. Type 2 diabetes mellitus constitutes about 90% of total diabetes.

Type II diabetes is characterized by a functional deficit of insulin due to an imbalance between insulin levels and insulin sensitivity as stated by Saeedi P et

al.,(2019)¹⁰ In recent years, the incidence of diabetes has been alarmingly increasing, and the treatment of diabetes imposes an enormous social and financial burden on society. The disease develops due to the complex integration of genetic and lifestyle factors. Type II diabetes is one of the complex diseases in which genetic components play an important role in the development of the disease. Das SK et al.,(2009) has stated that multiple lines of evidence support the fact that type II diabetes is a genetic disease. Familial aggregation of cases, increased concordance in monozygotic twins, variation in prevalence in different ethnic groups, all support the above fact regarding the genetic basis of the disease.^[11]

Identifying the genetic components of type 2 diabetes is one of the most significant areas of diabetes research. Identification of the diabetic genes (alleles) is essential for understanding of the disease, its prevention, complications and treatment.

John R. Petrie et al.,(2011) has stated in his study that genome wide association studies has identified 38 susceptibility loci for Type II diabetes mellitus.¹² The majority of these susceptibility loci code for proteins which influence beta cell function, which includes glucose-sensing, processing of pro insulin and insulin secretion. As stated by Jiang et al .,(2021) KCNQ1 gene, (potassium voltage-gated channel, sub-family, member 1) is associated with T2DM in various populations.¹³ KCNQ1 encodes a pore-forming sub unit of a voltage-gated potassium channel. Sun Q et al., (2012) has stated polymorphism in KCNQ1 (rs2237892) has been implicated as a risk factor for Type II diabetes.^[14]

Single nucleotide polymorphisms (SNPs) represent the most common form of genetic variation in the human genome and may influence an individual's susceptibility to various diseases. Among the polymorphisms identified in the KCNQ1 gene, rs2237892 has attracted considerable attention. This polymorphism, located within intron.^[15] of the gene, has been associated with impaired β -cell function and reduced insulin secretion. Several studies conducted in Japanese, Chinese, Korean, Indian, and European populations have demonstrated a significant association between the rs2237892 polymorphism and increased susceptibility to Type 2 diabetes mellitus, although ethnic differences in allele frequencies have produced variable findings across populations.

South India has one of the highest burdens of Type 2 diabetes in the country; however, relatively few studies have investigated the genetic contribution of KCNQ1 polymorphisms in this population. Identification of genetic determinants may facilitate early risk prediction, individualized preventive strategies, and a better understanding of disease pathogenesis. Therefore, the present study was undertaken to evaluate the association between the KCNQ1 (rs2237892) gene polymorphism and Type 2 diabetes mellitus among South Indian adults and to determine its potential role as a genetic determinant of disease susceptibility.

Aims And Objectives:

- To analyze the presence of single nucleotide polymorphism of KCNQ1 gene in Type II Diabetes mellitus patients and in healthy controls.
- To imply that single nucleotide polymorphism of KCNQ1 (rs2237892 genotype) as a genetic determinant for Type II diabetes mellitus

MATERIALS AND METHODS

Study Design and Study Setting: A hospital-based case-control study was conducted at K.A.P.V. Government Medical College and MGM Government Hospital, Tiruchirappalli, from September 2021 to August 2022, following approval from the Institutional Ethical Committee.

Study Population: The study included 90 South Indian adults aged 40–60 years, comprising 45 patients with established type 2 diabetes mellitus (cases) and 45 healthy non-diabetic individuals (controls). Cases were recruited from the Medicine Outpatient Department, while controls were selected from individuals attending screening for non-communicable diseases. Written informed consent was obtained from all participants.

Inclusion and Exclusion Criteria: Cases included type 2 diabetic patients aged 40–60 years, whereas controls comprised non-diabetic individuals within the same age group. Individuals with major chronic illnesses, including cardiac failure, chronic kidney disease, chronic liver disease and chronic lung disease, were excluded.

Clinical and Biochemical Assessment: All participants underwent detailed history taking, clinical examination, anthropometric assessment including height, weight and body mass index (BMI), and blood pressure measurement. Five millilitres of venous blood were collected under aseptic precautions. Two millilitres were collected in an EDTA tube for DNA extraction, while 3 mL was collected in a plain tube, centrifuged at $1000 \times g$ for 15 minutes, and serum was separated for biochemical investigations. Serum glucose, urea, creatinine, total cholesterol, HDL cholesterol and triglycerides were estimated using standard automated biochemical methods.

DNA Isolation: Genomic DNA was extracted from 2 mL of EDTA-anticoagulated whole blood using the G-Sure blood DNA isolation kit and spin-column method. The procedure involved sample lysis, DNA binding to the spin column, washing and elution. Purified DNA was stored at -20°C until PCR amplification.

PCR Amplification and Genotyping: The KCNQ1 rs2237892 region was amplified by polymerase chain reaction using the documented forward primer 5'-CTTGTCGCCCTTGTCACCCAC-3' and reverse primer 5'-GGCTTCCAGCCTCCAAGCTG-3'. The 25 μL PCR reaction contained Taq polymerase, DNA template, forward and reverse primers, dNTPs, MgCl_2 -containing buffer and distilled water. PCR

cycling consisted of initial denaturation at 95°C for 5 minutes, followed by 37 cycles of denaturation at 95°C for 30 seconds, annealing at 59.5°C for 15 seconds and extension at 72°C for 30 seconds, with a final extension at 72°C for 5 minutes. A 354-bp PCR product confirmed amplification.

Restriction Fragment Length Polymorphism

Analysis: Genotyping was performed using MspI restriction enzyme digestion. A 20 µL digestion mixture containing PCR product, MspI enzyme, NE buffer and autoclaved distilled water was incubated at 37°C for 4 hours. Digested products were separated by 1.8% agarose gel electrophoresis and visualized under UV illumination. The CC genotype showed 269-bp and 85-bp fragments, CT genotype showed 354-, 269- and 85-bp fragments, while the TT genotype showed an undigested 354-bp fragment.

Statistical Analysis: Data were analyzed using SPSS. Student's t-test was used for comparison of biochemical parameters between cases and controls, while the Chi-square test was used to assess genotype distribution. Hardy-Weinberg equilibrium was assessed, and logistic regression, odds ratios and 95% confidence intervals were calculated to evaluate the association between KCNQ1 rs2237892 polymorphism and type 2 diabetes mellitus. A p-value <0.05 was considered statistically significant, while p<0.001 was considered highly significant.

RESULTS

A total of 90 participants, comprising 45 type 2 diabetes mellitus cases and 45 healthy controls, were analyzed for KCNQ1 rs2237892 genotype distribution and its association with diabetes.

Table 1: Comparison of Age and BMI between Type 2 Diabetes Mellitus Cases and Controls

Parameter	Controls (n=45) Mean ± SD	Cases (n=45) Mean ± SD	t value	p-value
Age (years)	49.84 ± 5.661	50.96 ± 5.317	0.960	0.340
BMI (kg/m ²)	29.85 ± 3.71	28.00 ± 4.89	1.654	0.102

[Table 1] compares the age and BMI of patients with type 2 diabetes mellitus (T2DM) and healthy controls. The mean age was slightly higher among cases (50.96 ± 5.317 years) compared with controls (49.84 ± 5.661 years); however, this difference was not statistically significant (t = 0.960, p = 0.340).

Similarly, the mean BMI was 28.00 ± 4.89 kg/m² among cases and 29.85 ± 3.71 kg/m² among controls. The difference in BMI was also not statistically significant (t = 1.654, p = 0.102). Thus, the two groups were comparable with respect to age and BMI.

Table 2: Comparison of Blood Pressure and Glycaemic Parameters between Cases and Controls

Parameter	Controls (n=45) Mean ± SD	Cases (n=45) Mean ± SD	t value	p-value
Systolic BP (mmHg)	118.84 ± 10.724	123.36 ± 14.702	1.663	0.100
Diastolic BP (mmHg)	73.20 ± 6.444	79.33 ± 8.485	3.861	<0.001
Fasting blood sugar (mg/dL)	87.82 ± 7.542	152.24 ± 36.695	11.536	<0.001
Postprandial blood sugar (mg/dL)	129.22 ± 12.282	266.64 ± 55.822	16.129	<0.001

[Table 2] shows the comparison of blood pressure and glycaemic parameters between T2DM cases and healthy controls. The mean systolic blood pressure was higher among cases (123.36 ± 14.702 mmHg) than controls (118.84 ± 10.724 mmHg), although the difference was not statistically significant (t = 1.663, p = 0.100). In contrast, the mean diastolic blood pressure was significantly higher among cases (79.33 ± 8.485 mmHg) compared with controls (73.20 ± 6.444 mmHg), with a statistically significant difference (t = 3.861, p < 0.001).

Marked differences were observed in glycaemic parameters. Mean fasting blood sugar was substantially higher among cases (152.24 ± 36.695 mg/dL) than controls (87.82 ± 7.542 mg/dL), with a highly significant difference (t = 11.536, p < 0.001). Similarly, mean postprandial blood sugar was significantly higher in cases (266.64 ± 55.822 mg/dL) compared with controls (129.22 ± 12.282 mg/dL) (t = 16.129, p < 0.001). These findings confirm the expected significant difference in glycaemic status between the diabetic and control groups.

Table 3: Comparison of Lipid Profile between Type 2 Diabetes Mellitus Cases and Controls

Parameter	Controls (n=45) Mean ± SD	Cases (n=45) Mean ± SD	t value	p-value
Total cholesterol (mg/dL)	182.44 ± 17.082	251.70 ± 54.052	8.205	<0.001
HDL cholesterol (mg/dL)	39.53 ± 4.516	33.18 ± 5.642	5.900	<0.001
Triglycerides (mg/dL)	136.69 ± 15.39	157.16 ± 21.848	5.137	<0.001

[Table 3] compares the lipid profile between T2DM cases and healthy controls. The mean total cholesterol level was significantly higher among cases (251.70 ± 54.052 mg/dL) compared with controls (182.44 ± 17.082 mg/dL), with a highly significant difference (t = 8.205, p < 0.001). In contrast, mean HDL cholesterol was significantly lower among cases (33.18 ± 5.642 mg/dL) than controls (39.53 ± 4.516 mg/dL) (t = 5.900, p < 0.001).

Mean triglyceride levels were also significantly elevated among cases (157.16 ± 21.848 mg/dL) compared with controls (136.69 ± 15.39 mg/dL), with a statistically significant difference (t = 5.137, p < 0.001). Overall, the findings demonstrate an adverse lipid profile among individuals with T2DM, characterized by higher total cholesterol and triglyceride levels and lower HDL cholesterol levels.

Table 4: Distribution of KCNQ1 (rs2237892) Genotypes among Cases and Controls

KCNQ1 rs2237892 Genotype	Controls, n (%)	Cases, n (%)	Chi-square	p-value
CC	17 (37.8%)	6 (13.3%)	26.325	<0.0001
CT	24 (53.3%)	12 (26.7%)		
TT	4 (8.9%)	27 (60.0%)		
Total	45 (100%)	45 (100%)		

[Table 4] presents the distribution of KCNQ1 rs2237892 genotypes among T2DM cases and healthy controls. A marked difference in genotype distribution was observed between the two groups. The CC genotype was more frequent among controls, being present in 17 (37.8%) controls compared with only 6 (13.3%) cases. The CT genotype was also more common among controls [24 (53.3%)] than cases [12 (26.7%)].

In contrast, the TT genotype was substantially more frequent among T2DM cases, occurring in 27

(60.0%) cases compared with only 4 (8.9%) controls. The overall difference in genotype distribution was statistically highly significant ($\chi^2 = 26.325$, $p < 0.0001$). These findings indicate a significant association between the KCNQ1 rs2237892 genotype and T2DM in the study population, with the TT genotype occurring predominantly among diabetic cases, whereas the CC and CT genotypes were more frequent among controls.

Table 5: Allele Frequency Distribution of KCNQ1 (rs2237892) between Cases and Controls

Allele	Cases (n=90 alleles), n (%)	Controls (n=90 alleles), n (%)	Total	Chi-square	p-value
T allele	66 (73.3%)	32 (35.6%)	98	25.893	<0.0001
C allele	24 (26.7%)	58 (64.4%)	82		
Total	90 (100%)	90 (100%)	180		

[Table 5] demonstrates the allele frequency distribution of the KCNQ1 rs2237892 polymorphism among T2DM cases and healthy controls. The T allele was considerably more frequent among cases, accounting for 66 (73.3%) of the alleles, compared with 32 (35.6%) among controls. Conversely, the C allele was more frequent among controls [58 (64.4%)] than among cases [24 (26.7%)].

The difference in allele distribution between cases and controls was statistically highly significant ($\chi^2 = 25.893$, $p < 0.0001$). Thus, the T allele was markedly overrepresented among individuals with T2DM, whereas the C allele was more common among healthy controls. This finding further supports an association between the KCNQ1 rs2237892 polymorphism and susceptibility to T2DM in the study population.

DISCUSSION

Type 2 diabetes mellitus (T2DM) is a complex polygenic metabolic disorder resulting from interactions between genetic susceptibility and environmental and lifestyle factors. The identification of genetic variants that influence β -cell function and insulin secretion has therefore become an important area of diabetes research. The KCNQ1 gene, which encodes a voltage-gated potassium channel, has been identified as one of the susceptibility genes for T2DM. The rs2237892 polymorphism of KCNQ1 has been investigated extensively in different ethnic populations, although the magnitude and direction of association have varied between populations.^[15]

Age and BMI: In the present study, the mean age of diabetic cases was 50.96 ± 5.317 years, compared with 49.84 ± 5.661 years among controls. The two

groups were quite equivalent in terms of age, as the difference was not statistically significant ($p=0.340$) [Table 1]. Similarly, there was no statistically significant difference ($p=0.102$) in the BMI of patients and controls, which was 28.00 ± 4.89 kg/m² and 29.85 ± 3.71 kg/m². Therefore, significant variations in age or BMI were less likely to account for the observed genetic differences between the groups.

Because age is a known risk factor for type 2 diabetes and can be a confounding factor when comparing genotype frequencies, the similar age distribution is especially crucial in a genetic association research. T2DM is a genetically heterogeneous illness in which a variety of genetic and non-genetic variables combine to determine disease risk, according to Das and Elbein.^[11] In a similar vein, T2DM was defined by John R. Petrie et al. as a disorder involving complex interactions between genetic susceptibility, insulin resistance, β -cell dysfunction, and environmental factors.^[12] In an effort to lessen the impact of age, the participants in this study were chosen within the relatively narrow age range of 40–60 years. According to the thesis, there was no discernible age difference since the age groupings of the patients and controls were identical.

It is also interesting that the current study did not find a significant change in BMI. While being overweight is a significant risk factor for type 2 diabetes, genetic predisposition can also play a role in the development of the illness. Because the difference was statistically insignificant, the slightly higher mean BMI in the controls in this research should not be construed as evidence against the known link between obesity and diabetes. It's possible that the very small sample size hindered the detection of slight variations.

While systolic blood pressure did not differ significantly (123.36 ± 14.702 vs. 118.84 ± 10.724

mmHg; $p=0.100$), the current study showed a significant difference in diastolic blood pressure, with mean values of 79.33 ± 8.485 mmHg in cases compared with 73.20 ± 6.444 mmHg in controls ($p<0.001$). These results imply that greater diastolic blood pressure was specifically linked to diabetes in the study group. The results presented by John R. Petrie et al., who emphasised the intimate connection between diabetes, hypertension, and cardiovascular disease, are in line with this observation.¹² Due to common causes such as insulin resistance, endothelial dysfunction, neurohormonal activation, and vascular anomalies, diabetes and hypertension often coexist. With a very significant p-value, the thesis also found a strong correlation between diabetes and higher diastolic blood pressure.

As anticipated, persons with diabetes had significantly higher fasting and postprandial glucose levels. Postprandial blood glucose levels were 266.64 ± 55.822 mg/dL and 129.22 ± 12.282 mg/dL, respectively; mean fasting blood glucose levels were 152.24 ± 36.695 mg/dL in cases and 87.82 ± 7.542 mg/dL in controls. [Table 2] shows that both differences were statistically significant ($p<0.001$). These results demonstrate that the chosen patients had significantly aberrant glycaemic parameters and validate the metabolic difference between the diabetic and non-diabetic groups.

Significant metabolic differences between patients and controls were shown by the lipid profile study [Table 3]. Compared to controls (182.44 ± 17.082 mg/dL; $p<0.001$), total cholesterol was considerably greater in diabetes patients (251.70 ± 54.052 mg/dL). HDL cholesterol, on the other hand, was considerably lower in cases (33.18 ± 5.642 mg/dL) than in controls (39.53 ± 4.516 mg/dL; $p<0.001$). Additionally, cases had considerably higher triglyceride levels (157.16 ± 21.848 mg/dL) than controls (136.69 ± 15.39 mg/dL; $p<0.001$). These results are consistent with those of Chen et al., who found a link between hyperlipidaemia and type 2 diabetes and identified metabolic variables associated with hyperlipidaemia as significant predictors of diabetes risk.^[16] As a result, the current study shows a similar trend, with diabetes patients exhibiting an unfavourable lipid profile marked by elevated triglycerides and total cholesterol.

The findings of Goldberg, who defined diabetic dyslipidaemia as being marked by anomalies in lipid metabolism, including decreased HDL cholesterol, are likewise in line with the decrease in HDL cholesterol among diabetic individuals.^[17] The HDL cholesterol difference between patients and controls in the current investigation was extremely significant ($p<0.001$), indicating the existence of a typical diabetic dyslipidemic pattern [Table 3]. The findings reported by Alexopoulos et al., who highlighted that hypertriglyceridemia is widespread in diabetes and constitutes an essential component of diabetic dyslipidaemia, are also consistent with the considerably elevated triglyceride concentration seen among patients.^[18] Therefore, the current results are

in line with the more general metabolic profile linked to type 2 diabetes.

The main discovery of this investigation was that the distribution of the KCNQ1 rs2237892 genotype differed significantly between diabetes individuals and healthy controls [Table 4]. Six cases (13.3%) and 17 controls (37.8%) had the CC genotype, whereas 12 cases (26.7%) and 24 controls (53.3%) had the CT genotype. The TT genotype, on the other hand, was significantly more common in diabetes patients, appearing in 27 cases (60.0%) as opposed to just 4 controls (8.9%). The genotype distribution difference was statistically significant overall ($\chi^2=26.325$, $p<0.0001$).

This notable variation lends credence to a link between T2DM and the KCNQ1 rs2237892 polymorphism in the South Indian population under study. Specifically, the T allele may contribute to genetic predisposition to type 2 diabetes, as indicated by the significant enrichment of the TT genotype among diabetics.

The result is in line with previous research by Unoki et al.,^[19] who found that KCNQ1 mutations were susceptibility loci for T2DM in populations from East Asia and Europe. The current results also concur with Sun et al.'s meta-analysis, which showed a link between T2DM risk and KCNQ1 polymorphisms.^[14] In a similar vein, Li et al. found a favourable correlation between T2DM in Asian populations and the KCNQ1 rs2237892 C→T polymorphism in a meta-analysis of 15,736 individuals.^[20] Therefore, the direction of relationship observed by Li et al. is consistent with the significant rise in the TT genotype among patients in the current investigation. The revised meta-analysis by Jiang et al., which found that KCNQ1 rs2237892 was linked to T2DM susceptibility in a number of populations, including Japanese, Korean, Chinese, Indian, and European populations, further supports the findings.^[21] In particular, the authors highlighted a robust positive correlation between T2DM and rs2237892.

But not every study has yielded the same results. According to Han et al.'s meta-analysis, there was no evidence of a positive correlation between T2DM and KCNQ1 rs2237892 in the Asian population.^[22] Variations in ethnic origin, allele frequencies, sample size, genetic structure, and environmental exposures can all contribute to these disparities. Additionally, the thesis explicitly acknowledges that geographic and ethnic origin may have an impact on genotype and allele frequencies.

The link found at the genotype level was further supported by the allele-level analysis. In contrast to 32 of 90 alleles (35.6%) in controls, the T allele was found in 66 of 90 alleles (73.3%) in cases. In contrast, the C allele was found in 58 alleles (64.4%) in controls and 24 alleles (26.7%) in cases. [Table 5] shows that the allele distribution difference was extremely significant ($\chi^2=25.893$, $p<0.0001$).

Further evidence that this variant may be linked to an increased vulnerability to type 2 diabetes in the South Indian community under study comes from the

roughly two-fold greater frequency of the T allele among diabetic cases. The outcome is consistent with Li et al.'s meta-analysis, which found that the C→T mutation at rs2237892 is a susceptibility variable for type 2 diabetes in Asian populations.^[20] Additionally, it is in line with Jiang et al.'s findings that rs2237892 is linked to T2DM susceptibility in a variety of ethnic groups.^[13]

This connection might possibly be explained by a physiologically viable mechanism. A potassium channel that is expressed in pancreatic tissue is encoded by the KCNQ1 gene, and variations in this gene may affect potassium-channel function and, in turn, insulin secretion. According to the thesis, rs2237892 is a variation that may impede insulin release by altering potassium-channel function in pancreatic β-cells. Ashcroft, who emphasised the crucial involvement of potassium channels in pancreatic β-cell electrical activity and insulin secretion, has also addressed the functional significance of potassium channels to insulin secretion.^[23]

Overall Interpretation of KCNQ1 rs2237892 as a Genetic Determinant: When combined, the results from [Table 4 and 5] offer the most convincing proof of the genetic relationship this study looked at. Both the T allele and the TT genotype were significantly more common in diabetics than in controls. Additionally, the thesis presents logistic regression analysis that reveals an odds ratio of 4.98 (95% CI: 2.64–9.42; p=0.001) for the T allele, demonstrating significantly higher probabilities of T2DM among T allele carriers.

The suggested title, "Evaluation of KCNQ1 (rs2237892) Gene Polymorphism as a Genetic Determinant of Type 2 Diabetes Mellitus among South Indian Adults," is especially pertinent to this finding. The findings suggest that in this South Indian research community, the T allele and especially the TT genotype may be genetic risk factors for type 2 diabetes. Although the contradictory results reported by Han et al.,^[22] emphasise the significance of ethnic and population-specific genetic effects, the results are generally compatible with the data from Unoki et al.,^[19] Sun et al.,^[14] Li et al.,^[20] and Jiang et al.^[13]

The present study therefore adds population-specific evidence supporting the role of KCNQ1 rs2237892 in T2DM susceptibility. Nevertheless, the sample consisted of only 90 participants, and the original thesis itself recognizes the need for larger population-based studies to confirm the observed allele-frequency differences and establish the reproducibility of the association.

CONCLUSION

The present study demonstrated a significant association between KCNQ1 rs2237892 polymorphism and type 2 diabetes mellitus (T2DM) among South Indian adults. The T allele may have a role in genetic predisposition to type 2 diabetes, since

the TT genotype and T allele were much more common in diabetic patients. Along with reduced HDL cholesterol, cases also had substantially higher diastolic blood pressure, total cholesterol, triglycerides, and fasting and postprandial blood glucose. The results corroborate KCNQ1 rs2237892's possible function as a genetic determinant of type 2 diabetes. However, more extensive population-based research is needed to validate these results and demonstrate their wider application.

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