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The impact of Polymorphisms of rs689 and rs757110 in Familial Type 2 Diabetes: A Case-Control Study in the Iranian Population

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Abstract

Objective: Understanding the genetic basis of type 2 diabetes mellitus (T2DM) is essential in getting its etiology and designing effective preventive strategies. Evaluation of the association between the gene polymorphisms rs689A/T (*INS*) and rs757110C/A (ABCC8) and the susceptibility to T2DM within a group of individuals diagnosed with T2DM in Iran.

Materials and Methods: Blood samples were used for DNA extraction (200 with T2DM and 200 healthy controls). The quality and quantity of extracted DNA were assessed via ultraviolet spectrophotometry at 260 nm and 280 nm wavelengths. To identify specific alleles, primer sequences were manually designed using Primer3Plus, and the genotypes of rs689 (A>T) and rs757110 C>A were determined through ARMS-PCR. Statistical analysis was conducted using GraphPad Prism version 8.

Results: For rs689 individuals with the genotype (AA) were found to have a higher likelihood of developing diabetes (P= 0.001). Additionally, the frequency of the A allele was found to be higher in the patient group (0.13) compared to the control group (0.05). For rs757110 individuals with the genotype (CC) were found to have a higher likelihood of developing diabetes (P< 0.001). Additionally, the frequency of the C allele was found to be higher in the patient group (0.57) compared to the control group (0.39).

Conclusion: This study found that the frequency of AA and AT genotypes of rs689 and CC and CA genotypes of rs757110 are associated with T2DM risk.

Keywords: Diabetes, ARMS-PCR, rs689, rs757110

QR Code:

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Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial group of conditions distinguished by inadequate insulin secretion and/or impaired insulin sensitivity, contributing to the dysregulated metabolism of carbohydrates, lipids, and proteins (1). T2DM accounts for approximately 95% of all diabetes cases (2). The global prevalence of T2DM has been gradually increasing in recent decades, and it is projected to affect 9.9% of the world population by 2045, which constitutes a significant and unsustainable burden on global health (3,4). Despite the well-established benefits of lifestyle modifications and pharmacological treatments in preventing and managing T2DM, there is still a concerning rise in its prevalence (5-7).

Recent studies have provided evidence supporting the concept that T2DM is significantly impacted by genetic components (8-11). Notably, research has shown that individuals of Indian descent exhibit a higher susceptibility to insulin resistance compared to Europeans of similar age and body mass index (7,12). This observation suggests the presence of population-specific genetic elements play a substantial role in the pathogenesis of T2DM (13,14). Understanding the genetic basis of this disease is crucial in comprehending its etiology and designing effective preventive strategies (15). With advancements in genotyping and sequencing technologies, scientists have successfully identified Single Nucleotide Polymorphisms (SNPs) as genetic variants associated with T2DM and related glycemic traits. Moreover, researchers have explored the potential of combining these genetic risk variants into a composite score, which can enhance the prediction of diabetes in individuals beyond the information provided by clinical risk factors alone (16,17). The significance of genetic factors in the development of T2DM is underscored by these findings and emphasizes the need for further investigation into the role of genetics in disease prevention.

The *INS* gene is responsible for encoding insulin, a crucial hormone involved in regulating blood sugar levels. Following the removal of the precursor signal peptide, proinsulin undergoes post-translational cleavage to form three distinct peptides (18,19). Once insulin binds to the insulin receptor (INSR), it triggers the uptake of glucose by cells in the body. An adjacent gene known as *INS-IGF2* shares overlapping regions with the *INS* gene at the 5' end and with the IGF2 gene at the 3' end (20). Research studies have indicated that the insulin gene, located at the insulin-dependent diabetes mellitus 2 gene (IDDM2) locus, ranks as the second most significant genetic locus associated with T1DM. The risk linked to the IDDM2 locus is attributed to a specific haplotype characterized by some polymorphisms including a SNP at the rs689 (A>T) site (21,22).

The *ABCC8* gene encodes a protein classified within the ATP-binding cassette (ABC) transporter superfamily. Deficiencies in this protein due to mutations in the *ABCC8* gene have been linked to hyperinsulinemic hypoglycemia of infancy, characterized by unregulated and excessive insulin secretion in affected patients (23). Furthermore, mutations in the *ABCC8* gene have also been implicated in non-insulin-dependent diabetes mellitus type II, a condition characterized by defective insulin secretion (24). One of the significant polymorphisms in the *ABCC8* gene, rs757110 (C>A), located in exon 33, has been identified as playing a crucial role in gene function. Research studies have demonstrated that different genotypes of the rs757110 polymorphism can impact the function of the *ABCC8* gene, potentially leading to various phenotypic conditions, including T2DM (25-27). This highlights the importance of understanding the genetic polymorphisms in the *ABCC8* gene and their implications in T2DM.

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This research aimed to evaluate the relationship between the gene polymorphisms rs689A/T (*INS*) and rs757110C/A (*ABCC8*) and the susceptibility to familial T2DM within a group of individuals diagnosed with T2DM in Iran. This investigation builds upon the results obtained from a comprehensive prior study conducted by our team (5).

Material and Methods

Sample preparation

The research participants were selected from the Yazd Center for Diabetes, with a total of 400 individuals (200 with T2DM and 200 healthy controls) being included in the study consecutively following thorough clinical assessments conducted by the collaborating clinical team. The recruited participants were in the age range of 30 to 65 years (43% and 56% of the participants in the control and diabetic groups were male). Inclusion criteria for the T2DM group were based on the diagnostic standards designated by the World Health Organization as well as family history of diabetes in first-degree relatives (at least 3 affected individuals). Exclusion criteria for the study encompassed individuals with gestational diabetes, T1DM, hepatic or renal dysfunction, secondary diabetes, maturity-onset diabetes of the young, cardiac anomalies, malignant disorders, uncontrolled hypertension, hematological conditions, consumption of medications impacting glucose metabolism, psychosis, autoimmune diseases, anti-obesity drug usage, and influential gastrointestinal absorption issues. The control group was selected based on glycated hemoglobin (HbA1c) <5.7%, fasting blood glucose levels (<126 mg/dl), and no family history of diabetes (28, 29). All research activities adhered to 'The Code of Ethics of the World Medical Association' (Declaration of Helsinki). Prior to enrollment, the research process was elucidated to the contributors, and written informed consent was acquired.

The study subjects' clinical information was collected from their medical histories. Expert examiners conducted an anthropometric assessment of the participants. No significant difference was observed in the the documented blood chemistry parameters containing HbA1c, fasting plasma glucose, LDL and HDL cholesterol, total cholesterol, and triglycerides. Self-reporting was utilized to gather data on lifestyle factors, including smoking, diet, and alcohol consumption.

DNA extraction, allele-specific PCR reaction, and data analysis

Blood specimens were employed for DNA extraction utilizing the SimEX^{TM} Blood DNA Extraction Kit (Simbiolab Company Mashhad, Iran) under the provider's guidelines. The quantity and quality of obtained DNA were calculated via ultraviolet spectrophotometry at 260 nm and 280 nm wavelengths. The presence of high molecular weight DNA was confirmed by agarose gel electrophoresis (1%). To identify specific alleles, primer sequences were manually designed using Primer3Plus(https://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi), and the genotypes of rs689 (A>T) and rs757110 C>A were determined through ARMS-PCR (Table 1). The amplified PCR products were subsequently visualized using gel electrophoresis for further analysis.

Table 1. Primers sequences

rs	Primer	Product
rs689 ***INS***	rs689-F-N: CAGCCTGCCTCAGCCCTGCCTCTCT rs689-F-M: CAGCCTGCCTCAGCCCTGCCTCTCA rs689-R: AGGTGTTGGTTCACAAAGGCTGCG rs689-F-Ext: GGCCCTAATGGGCCAGGCGGCA	136 413
rs757110 ***ABCC8***	rs757110-F-N: TGCTGAAGCACGTCAATGCCCTCGTCG rs757110-F-M: TGCTGAAGCACGTCAATGCCCTCGTCT rs757110-R: GGGCCCCCACAGGCCCAGGGCAG rs757110-F-Ext TAGCTGTGGCCCATGCCTGGTGG	201 336

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Statistical analysis

The Hardy-Weinberg equilibrium was employed to assess the adequacy of fit through a chi-square test for genotype distribution. Mean ± standard deviation was used to display quantitative variables. A level of $P<0.05$ (defined using a two-tailed test) was considered statistically significant. Statistical analysis was done with GraphPad Prism 8 software.

Ethical considerations

This study has been evaluated and approved by the Research Ethics Committees of Mashhad Academic Center for Education, Culture and Research (IR.ACECR.JDM.REC. 1402.017).

Results

Some demographic and biochemical characteristics of the participants are summarised in Table 2.

PCR-ARMS reactions were conducted following the confirmation of DNA extraction accuracy. Allele-specific primers, for normal and altered alleles, were initially set for each polymorphism. Subsequently, the external control primer was incorporated with these primers, and the final reaction was carried out. The outcomes of the final reactions for each polymorphism can be observed in Figure 1.

The analysis of the rs689 polymorphism frequency in both the patient and control groups revealed a noteworthy finding. Specifically, individuals with the genotype (AA) were found to have a higher likelihood of developing diabetes. This conclusion was drawn based on the observation that the number of diabetes patients with AA and AT genotypes was significantly greater than the control group with the same genotypes ($P=$ 0.005) as presented in Table 3. Additionally, it was observed that the prevalence of the A allele was greater in the T2DM group (0.13) compared to the control group (0.05) as indicated in Table 4. These discoveries indicate a potential link between the rs689 polymorphism and an increased risk of diabetes.

The analysis of the rs757110 polymorphism frequency in both the patient and control groups revealed a noteworthy finding. Specifically, individuals with the genotype (CC) were found to have a higher likelihood of developing diabetes. This conclusion was drawn based on the observation that the number of diabetes patients with CC and CA genotypes was significantly greater than the control group with the same genotypes ($P<$ 0.001) as presented in Table 5. Table 6 shows that the patient group had a higher frequency of the C allele (0.57) compared to the control group (0.39). This discrepancy in allele frequency indicates a probable association between the rs757110 polymorphism and increased susceptibility to diabetes.

Discussion

To date, research has been conducted on the significance of genetic variations in the *INS* and *ABCC8* genes in T2DM and related conditions. Several pivotal studies have been discussed in the following.

In 2016, Sokhi et al. conducted a case-control study focusing on the correlation between various polymorphisms, such as rs689 of the *INS* gene, and T2DM within a population residing in northwest India.

Table 2. Demographic and biochemical characteristics of the participants

Variable	T2DM Mean(±SD)	Control Mean(±SD)	Adjusted *P*-Value
Age (Year)	54.31 (±3.12)	51.57 (±2.21)	0.28
BMI (Kg/m^2)	26.36 (±3.15)	24.14(±2.65)	0.54
HbA1c	8.13 (±1.15)	5.16 (±0.25)	0.001
FBS (mg/dl**)**	177.17 (±12.32)	82.16 (±11.21)	<0.0001
LDL (mg/dl**)**	135.21 (±14.31)	104.11 (±11.66)	<0.0001
HDL (mg/dl)	48.22 (±7.11)	42.35 (±6.35)	0.001
TG (mg/dl)	141.36 (±25.16)	129.25 (±14.14)	<0.0001

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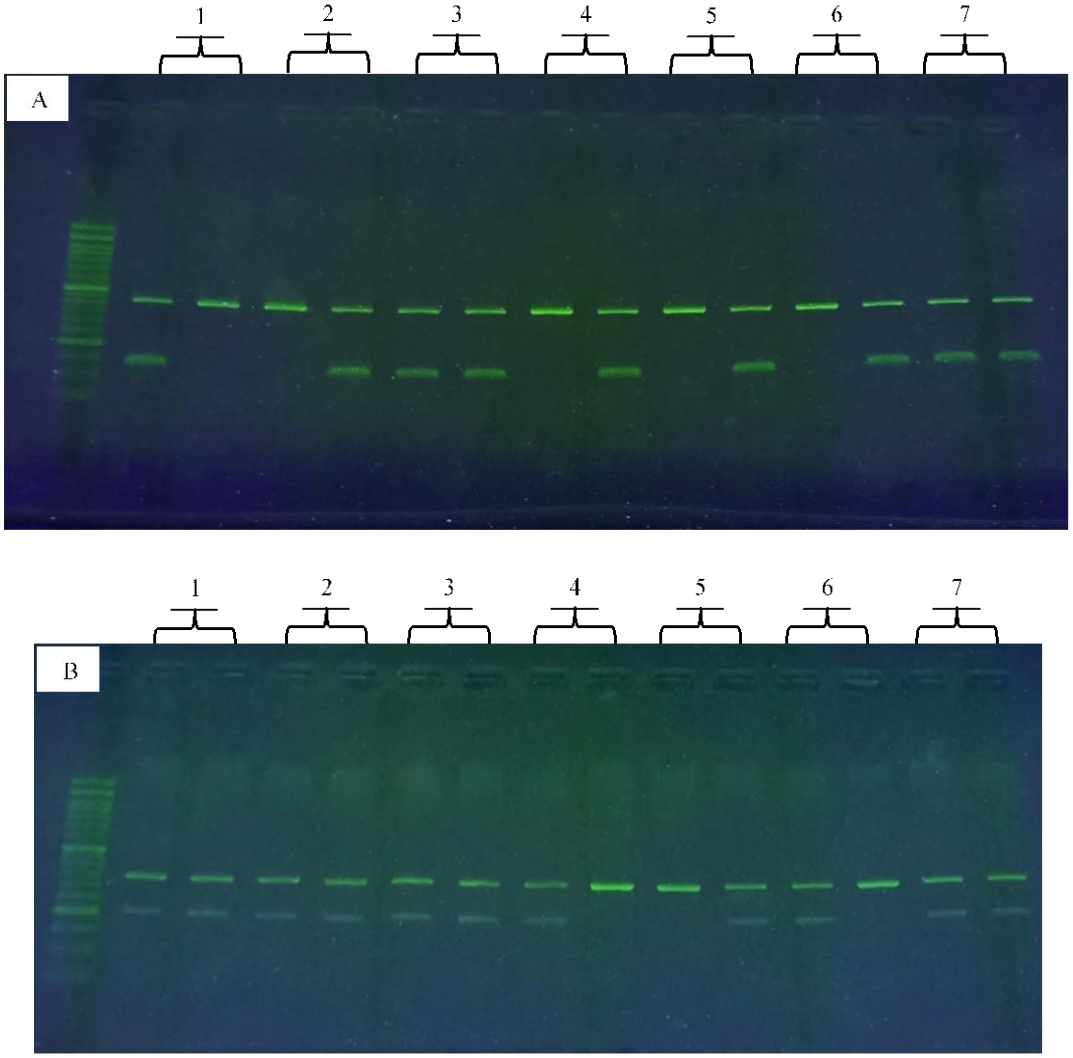

Figure 1. A; rs689, sample 1 normal homozygous, samples 2, 4, 5, and 6 mutant homozygous, samples 3 and 7 heterozygous (50 pb marker). B; rs757110, samples 4 and 6 normal homozygous, sample 5 mutant homozygous, samples 1, 2, 3, and 7 heterozygous (50 pb marker).

Table 3. Comparison of the frequency of the rs689 polymorphism in case and control groups

Genotype	Control group Observed		Case group Observed		Chi-square test Chi-square	*P*-Value
	No.	Percent	No.	Percent		
AA	1	1	7	5	10.48	0.005**
AT	12	8	25	17		
TT	137	91	118	78		

**: The frequency of the AA and AT genotypes of the rs689 polymorphism was higher in the case group than in the control group (*P*-value = 0.005).

The study encompassed 1216 cases of T2DM and healthy controls from four distinct ethnic groups (Jats, Sikhs, Baniyas, and Brahmins) in northwest India. The researchers specifically chose three polymorphisms, namely rs689, rs1799816, and rs1799999, for detailed examination. To determine the genotype frequencies, the research team

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utilized the PCR-RFLP method. The statistical analysis of Sokhi et al.'s study revealed a considerable correlation between the rs689 polymorphism and the sensitivity to T2DM across all three ethnic groups studied (30). Consequently, the outcomes of Sokhi et al.'s investigation regarding the link between rs689 and T2DM in a subset of the Indian population support the results of the present work, underscoring the pivotal role of rs689 in the development of T2DM.

Krischer et al. conducted an extensive study in 2022 that aimed to identify predictive factors for the onset of autoimmune damage and its progression in youth diabetes. In this study, they highlighted the role of a large number of environmental and genetic factors, including rs689. Their results indicated that the A allele of rs689 polymorphism in T1DM is related to primary autoimmune defects related to insulin production and can be important as a predictive factor (31). The results of Krischer et al.'s study also implicitly confirm the findings of the present study. According to the findings of Krischer et al.'s study, the presence of the A allele of the rs689 polymorphism can increase the risk of T1DM, and this overlaps with the findings of the present study, which reached similar results concerning T2DM.

The rs689 polymorphism of the *INS* gene has been extensively studied concerning T1DM, while its role in T2DM has received less attention. However, a comprehensive review of existing studies highlights the significance of various genotypes of the rs689 polymorphism in both T1DM and T2DM (32).

The rs689 polymorphism is a subject of significant interest due to its potential impact on the insulin gene (33). It is believed that this polymorphism, which is located at the end of intron 1 of the *INS* gene, may disrupt the splicing process by interfering with intron removal. This disruption can ultimately lead to defects in the production and function of insulin. Notably, the rs689 polymorphism is located near the splicing sequence (AG) at the 3' end of the intron.

To gain a deeper interpretation of the task of rs689 in T1DM and T2DM, further comprehensive investigations are required, particularly studies that explore the function of different genotypes in laboratory models. These complementary studies have the potential to shed light on the molecular pathway through which rs689 influences diabetes development.

Table 4. rs689 allele frequency

Variable	Allele A frequency	Allele T frequency
Control group	0.05	0.95
Case group	0.13	0.87

The frequency of the A allele was higher in the case group than in the control group. The frequency of the T allele in the patient group was lower than in the control group.

Table 5. Comparison of the frequency of the rs689 polymorphism in case and control groups

Genotype	Control group Observed		Case group Observed		Chi-square test	
	No.	Percent	No.	Percent	Chi	*P*-value
CC	21	14	45	30	20.21	<0.001**
CA	74	49	80	53		
AA	55	37	25	17		

**The frequency of the altered genotype of this polymorphism (AA) in the case group was significantly lower than the control group (*P*-Value< 0.001).

Table 6. rs757110 allele frequency

Variable	Allele A frequency	Allele C frequency
Control group	0.61	0.39
Case group	0.43	0.57

The frequency of the C allele in the case group was higher than in the control group. The frequency of the A allele in the case group was lower than in the control group.

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The *ABCC8* gene contains the rs757110 polymorphism, which is also referred to as Ala1369Ser and is located in exon 33. In a examination accompanied by Hamming et al. in 2009, it was demonstrated that the coexistence of two polymorphisms in individuals with T2DM alters the sensitivity of ATP-sensitive potassium channels to ATP and sulfonylurea (34). The *ABCC8* gene encodes a protein that belongs to the ATP transporter family and is involved in the exchange of various molecules across cell membranes. This protein serves as a regulator for ATP-sensitive potassium channels and insulin secretion. Research has implied that the expression of the *ABCC8* gene is elevated in patients with T2DM compared to healthy individuals (35). Consequently, any modification in the coding genes of the potassium channel subunit, including ABCC8, can disrupt insulin secretion and consequently impact glucose homeostasis.

A research study conducted in 2019 by Ebid et al. aimed to explore the impact of certain genetic polymorphisms, specifically rs757110 of the *ABCC8* gene, on the efficacy of a combined treatment involving metformin and glimepiride in individuals with T2DM from Egypt. The experiment strived to investigate how these genetic variations influenced the effectiveness of the treatment regimen. The research team highlighted in their study that despite the higher prevalence of the CC genotype in individuals with T2DM compared to control individuals in the Egyptian population, there was no observed association between the prevalence of this genotype and treatment response (26). The current study conducted on the population of Yazd province supports the findings of Ebid et al.'s study concerning the correlation between the CC genotype of the rs757110 polymorphism of the *ABCC8* gene and T2DM.

In a related study conducted in 2022, Tran et al. examined the Vietnamese population with T2DM to discover the probable link between SNPs of *KCNJ11* and *ABCC8* genes (rs757110) and T2DM. The investigators performed a cross-sectional study involving 404 individuals, consisting of 202 patients with T2DM and 202 non-diabetic controls. The findings of their study indicated that there was no statistically significant association between various genotypes of rs757110 and T2DM within the Vietnamese population (36). Hence, it is not surprising that the prevalence of various genotypes of polymorphism could have varying associations with disease risks across different populations. The research conducted by Tran et al. on the rs757110 polymorphism and its link to T2DM contradicts the findings of the current study, as well as the study by Ebid et al. on the Egyptian population. It is important to note that both Tran et al. and the present study utilized the ARMS method to analyze the genotypes of rs757110, with conflicting results, highlighting the impact of population-specific characteristics on polymorphism studies.

Conclusion

This research revealed that the frequency of AA and AT genotypes of rs689 polymorphisms of the *INS* gene was notably elevated in individuals with T2DM compared to the control group. Furthermore, the A allele was found to be more prevalent in the population with T2DM than the T allele. Consequently, it is suggested that the presence of the A allele in rs689 of the *INS* gene may be linked to an increased susceptibility to T2DM. Additionally, the study indicated that the frequency of CC and CA genotypes of rs757110 polymorphism of the *ABCC8* gene was higher in individuals with T2DM than in the control group. Moreover, the C allele was more common in the population with diabetes than the A allele. Thus, it is proposed that the presence of the A allele in rs689 of the *INS* gene and the presence of the C allele in rs757110 of the *ABCC8* gene are correlated with a heigher risk of T2DM in the population of Yazd province.

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Conflict of Interest

All authors declare that they have no conflicts of interest to disclose.

Authors' contributions

MY.V.M.: conceived the original idea. A.H. and A.Kh.: have performed the experimental tests. MY.V.M. and A.J: supervised the project. A.H. and A.Kh. wrote the manuscript with support from MY.V.M. and A.J.

All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the study, and read and approved the final manuscript.

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