Computational Analysis of ABCC8 and KCNJ11 Gene Variants in Type 1 Diabetes

Salsabeel Mohammed Abdallha, Yasir Adil Jabbar Alabdali and Mohammed Qasim Waheeb
Department of Biology, College of Science, Al Muthanna University, 66001 Samawah, Iraq
{salsabeelmoh, yasir.alabdali, mhmadkas}@mu.edu.iq

Keywords: ABCC8 Gene, KCNJ11 Gene, T1D, Lipid Profile.

Abstract: Type 1 diabetes (T1D) is an autoimmune disease characterized by progressive destruction of pancreatic β-cells and chronic hyperglycemia. Genetic variants in ATP-sensitive potassium (K-ATP) channel genes, including ABCC8 and KCNJ11, may influence insulin secretion and susceptibility to diabetes. This study aimed to evaluate the association of ABCC8 rs1799854, ABCC8 rs1801261, and KCNJ11 rs5219 polymorphisms with T1D risk and related clinical and biochemical parameters in children. A case-control design was used, including 60 T1D patients and 60 age- and sex-matched healthy controls recruited between November 2024 and February 2025. Genomic DNA was extracted from peripheral blood, and genotyping was performed using PCR-RFLP for ABCC8 variants and ARMS-PCR for KCNJ11. Clinical and biochemical parameters, including BMI, lipid profile, HbA1c, and random blood glucose, were measured using standard automated methods. Statistical analysis included chi-square tests, t-tests, and ANOVA, with odds ratios (ORs) and 95% confidence intervals (CIs) used to estimate associations. The heterozygous CT genotypes of ABCC8 rs1799854 and KCNJ11 rs5219 were significantly associated with increased T1D risk (OR = 3.27, $p = 0.003$; OR = 6.10, $p < 0.0001$). In contrast, the ABCC8 rs1801261 TT genotype showed a protective association with T1D (OR = 0.22, $p = 0.013$). Significant genotype-related differences were observed in BMI, HDL cholesterol, HbA1c, and glucose levels. These findings suggest that ABCC8 and KCNJ11 polymorphisms may contribute to T1D susceptibility and metabolic variation in affected children. However, larger studies are required to confirm these associations.

1 INTRODUCTION

Type 1 Diabetes Mellitus (T1D) is an immune-mediated condition involving the destruction of pancreatic β-cells resulting in insulin deficiency and chronic hyperglycemia [1]. Although patients get diagnosed after the clinical manifestations of hyperglycemia appear, the first stage of the disease is islet autoimmunity, a phase marked by the continuous presence of autoantibodies targeting pancreatic islet antigens, which usually starts in early childhood and can have a remitting-relapsing course before the onset of diabetes [2], [3]. Globally, T1D incidence is rising, especially in patients under the age of 15, 15-20% of new diagnoses are identified in children under the age of 5 [4]. Children with T1D often exhibit signs of polyuria, polydipsia, and weight loss. In some acute cases, children might present with diabetic ketoacidosis [5]. Recently, several reports have highlighted the interaction between environmental factors (e.g., viral infections, diet) and genetic factors in triggering β-cell autoimmunity [6]. Genetic predisposition of several loci involved in β-cell functionality and insulin secretion are significant plays a crucial role in disease onset and progression [7]. Genome-wide association studies have found more than 50 loci associated with the development of type 1 diabetes, particularly those implicated in immunological modulation (e.g., HLA class II) and β-cell function (e.g., PTPN22, IL2RA) [8]. At the molecular level, glucose-stimulated insulin secretion from β-cells is tightly controlled by ATP-sensitive potassium (K-ATP) channels are hetero-octameric structures made up of four sulfonylurea receptor 1 (SUR1) subunits that (encoded by ABCC8) and four Kir6.2 inward-rectifier subunits (encoded by KCNJ11), which regulates glucose-stimulated insulin release [9], [10]. Under low glucose conditions, K-ATP channels stay open, keeping the membrane hyperpolarized, which increases ATP/ADP ratios when glucose enters. Subsequently, this leads to the closure of the channel,

depolarization of the membrane, opening of voltage-gated Ca2+-channels, and consequent insulin granule exocytosis [11]. Single-nucleotide polymorphisms (SNPs) in ABCC8 (e.g., rs1799854 and rs1801261) and KCNJ11 (e.g., rs5219) have been widely associated with altered channel activity, β-cell excitability, and risk of developing diabetes in diverse populations [9], [10]. The KCNJ11 rs5219 (E23K) variant, for example, enhances channel sensitivity to ATP, whilst ABCC8 rs1799854 alters SUR1 expression levels; both mechanisms affect insulin release dynamics [12]. Although many studies have explored the role of genetic polymorphisms of K-ATP channels in T2D [10], [11], their role in T1D remains poorly understood, and data on the distribution of these polymorphisms and their clinical impact among pediatric T1D patients in Iraq are scarce. The object of this study was to investigate the various genotype frequencies of ABCC8 rs1799854, ABCC8 rs1801261, and KCNJ11 rs5219 in children with T1D from Al Muthanna Province, and to examine their associations with clinical (e.g., body mass index (BMI)) as well as biochemical markers (e.g., lipid profile, glycated hemoglobin (HbA1c), random blood sugar (RBS)). Understanding these genetic influences may shed light on disease heterogeneity and identify biomarkers for risk stratification and personalized management in this population

2 SUBJECT AND METHODS

2.1 Ethical Approval

The Approval of this study was given by the Al-Muthanna Health Department at the College of Science at Al-Muthanna University. Participation was voluntary, and written informed consent was obtained from each child's legal guardian before sample collection.

2.2 Study Population

Between November 2024 and February 2025, (sixty children ≤ 15 years) recruited for the study from the Endocrinology and Diabetes Center at Al-Hussein Teaching Hospital in the Al-Muthanna Governorate, who had been diagnosed with T1D, based on the American Diabetes Association (ADA) classification [13]. Information related to patients: age, sex, residential location, family history, weight, and height were recorded. A group of 60 healthy children matched for age and sex, who had no family history of diabetes and normal range of HbA1c levels, was enrolled. Exclusion criteria involved children with thyroid problems, hepatic or renal impairment, type 2 diabetes, secondary or monogenic types of diabetes, or intake of drugs known to affect glucose metabolism. Further exclusion included children with autoimmune diseases, chronic illnesses, or recent infections.

2.3 Biochemical Measurements

Venous blood (5 mL) were collected from children and 2 mL were collected into (EDTA tubes) for HbA1c measurement and genomic DNA extraction. HbA1c was quantified using a High Fact automated analyzer (HMG, Germany). The remaining (3ml) were placed in gel tubes and used to assess lipid profiles such as triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), and determined by a Cobas c111 analyzer (Roche Diagnostics, Germany).

2.4 Genotyping

Using the Wizard® Genomic DNA Purification Kit (Promega, USA) genomic DNA was isolated from 2 millimetres of whole blood, following the manufacturer guidelines. Gel electrophoresis on a 2% agarose gel stained with Ethidium Bromide (15 min at 100V) was then used to confirm integrity and concentration of DNA, followed by UV visualization. Samples of DNA were kept at -20°C.

The genotyping of the ABCC8 gene (rs1799854) and the ABCC8 gene (rs1801261) was carried out using the PCR-RFLP methods, employing primer sequences and restriction enzymes as previously published (12). Each PCR sample contained 25µl GoTaq® Green PCR mix (Promega, USA), 2.5µl forward and reverse primers (Alpha AND, Canada), 5µl genomic DNA, and 15µl nuclease-free water [14]. After being purified by using the Wizard® SV Gel and PCR Clean-Up System (Promega, USA), the amplified products were digested for two hours at 37 °C with either PstI (Jena Bioscience, Germany) for the rs1799854 or BsiEl restriction enzyme (Thermo Scientific, Lithuania) for the rs1801261. Following digestion, the products were separated on 2% agarose gel that had been stained with Ethidium Bromide, electrophoresed for 30 min at 100V, and visualized under ultraviolet light [15]. As previously reported, the Amplification Refractory Mutation System (ARMS-PCR) method was used to genotype the KCNJ11 rs5219 polymorphism using four allele-

specific primers (12). To ascertain genotype, ARMS-PCR products were electrophoresed on a 2% agarose gel (30 minutes at 100V), stained with Ethidium Bromide, and UV-visualized to observe bands.

2.5 Statistical Analysis

All statistical analyses were carried out using SPSS software (version 27.0.) Continuous variables (BMI, lipid levels, HbA1c, and RBS) are presented as mean ± standard deviation (SD), whilst categorical variables (genotype and allele frequencies) were expressed as frequencies and percentages. Glycemic and lipid profile parameters were compared between genotype groups by an independent-samples t-test or one-way ANOVA. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of association between each genotype and T1D risk. Deviation from the Hardy-Weinberg equilibrium in patients and controls was assessed by χ^2 goodness-of-fit. A p-value < 0.05 was considered statistically significant.

3 RESULTS

3.1 Social-Demographic Profile for T1D

A total of 120 subjects were enrolled in the study: 60 patients with (T1D) and 60 non-diabetic healthy children. T1D patients aged 9.68 ± 2.95, with a duration of disease diagnosis of 3.05 ± 2.36 years. The sex distribution comprised 28 males (46.7%) and 32 females (53.3%). Regarding residential patterns, T1D predominantly lived in rural areas (58.3%), whilst 41.7% in urban areas. A positive family history of diabetes was reported in nearly half of T1D patients (48.3%) (Table 1).

Table 1: Demographic features of T1D patients.

		Type-1 diabetes
Age [mean ± SD]		9.68 ± 2.95
Sex [n (%)]	Male	28 (46.7%)
	Female	32 (53.3%)
Residence [n (%)]	Urban	25 (41.7%)
	Rural	35 (58.3%)
Family history [n (%)]	Yes	29 (48.3%)
	No	31 (51.7%)
Duration of diabetic [mean ± SD]		3.05 ± 2.36

3.2 Comparison of Clinical and Biochemical Parameters in T1D Patients vs Control

Table 2 compares clinical and biochemical parameters between T1D patients and non-diabetic controls. T1D patients had significantly lower body mass index (BMI) than controls (16.81±2.14 vs 19.05±3.12; p<0.0001). Serum TC and HDL were also significantly lower in T1D (TC: 145.71±52.01 vs 170.57±18.58 mg/dL, p=0.001; HDL 44.21±8.82 vs 48.90±6.29 mg/dL, p=0.001). Conversely, glycaemic indices were markedly higher in T1D: Average HbA1c was 9.63±2.37% vs 5.04±0.55% in controls (p<0.0001), and random blood sugar (RBS) was 306.17±137.07 vs 99.43±15.55 mg/dL (p<0.0001). Other parameters (TG and LDL) showed no significant differences.

Table 2: Biochemical and clinical parameters in T1D patients versus controls.

	T1D vs. control		p-value
		Mean ± SD	
BMI	T1D	6.813 ± 2.14	<0.0001*
	Control	19.05 ± 3.12	
TG	T1D	127.75 ± 60.11	0.162
	Control	115.25 ± 33.36	
TC	T1D	145.71 ± 52.01	0.001*
	Control	170.57 ± 18.58	
HDL	T1D	44.21 ± 8.82	0.001*
	Control	48.90 ± 6.29	
LDL	T1D	101.71 ± 38.47	0.467
	Control	97.69 ± 18.36	
HbA1c	T1D	9.63 ± 2.37	<0.0001*
	Control	5.04 ± 0.55	
RBS	T1D	306.17 ± 137.07	<0.0001*
	Control	99.43 ± 15.55	

3.3 Genotyping of ABCC8 and KCNJ11 Polymorphisms by PCR-Based Methods

Gel electrophoresis analysis of ARMS-PCR products for the KCNJ11 rs5219 C>T gene polymorphism (Fig. 1) revealed two distinct genotypes based on PCR fragment sizes. The CC genotype was represented by a single band at 162 bp, corresponding to the wild-type allele, whilst the CT genotype displayed two bands at 349 bp and 162 bp, indicating the presence of both alleles. DNA ladder on the left side of the gel, ranging from 100 to 1000 bp, was used for molecular weight estimation. The banding profiles

demonstrated that the CT heterozygous genotype was the most prevalent among the tested samples.

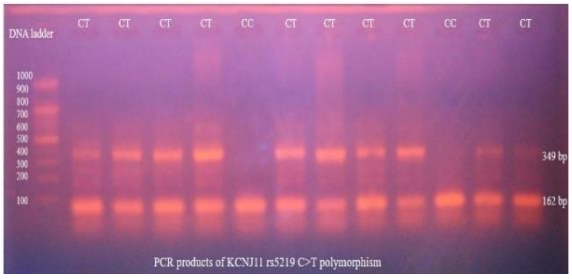

Figure 1: Genotyping of KCNJ11 rs5219 by ARMS-PCR.

Gel electrophoresis of the ABCC8 rs1799854 gene PCR product (Fig. 2a) on a 2% agarose gel showed specific amplification of a 248 bp fragment of the ABCC8 gene. The DNA ladder (100–1000 bp) included in the gel served as a reference for fragment size determination.

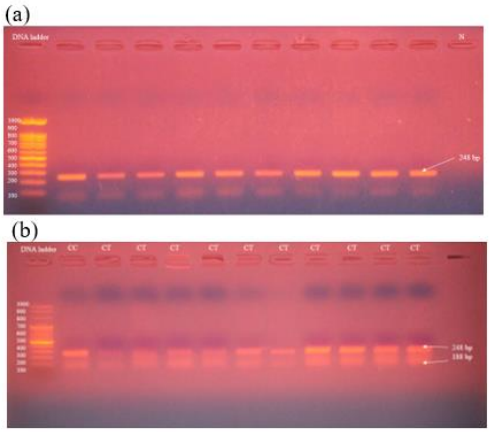

Figure 2: Genotyping of ABCC8 rs1799854 and rs1801261 polymorphisms by PCR and PCR-RFLP analysis: a) gel electrophoresis of ABCC8 rs1799854 PCR product showing a 248 bp fragment amplification; b) PCR-RFLP analysis of ABCC8 rs1799854 (PstI digestion) demonstrating CC (248 bp) and CT (248/188 bp) genotypes.

PCR-RFLP analysis of the ABCC8 rs1799854 C>T gene polymorphism using PstI restriction enzyme digestion (Fig. 2b) revealed two distinct genotypes. The CC genotype showed a single undigested band at 248 bp, whilst the CT genotype exhibited two bands at 248 bp and 188 bp, indicating the presence of both alleles. DNA ladder (100–1000 bp), located on the left side of the gel were used for estimating fragment sizes. The heterozygous CT genotype was the most frequently observed among the analyzed samples.

PCR amplification of ABCC8 rs1801261, visualized on a 2% agarose gel, showed a specific 158 bp product (Fig. 3a). DNA ladders (100–1500 bp) on the left and right sides of the gel served as molecular weight standards.

PCR-RFLP genotyping of the ABCC8 rs1801261 C>T polymorphism following BsiEI digestion (Fig. 3b) identified three distinct genotypes based on fragment sizes after enzymatic digestion. The CC genotype produced a single 122 bp band, indicating complete digestion. The TT genotype showed a single undigested band at 158 bp, whilst the CT genotype showed both 158 bp and 122 bp bands, indicating the presence of both alleles. DNA ladders (100–1000 bp), loaded on both sides of the gel, and were used for fragment size reference. The heterozygous CT genotype was the most frequently detected among the analysed samples.

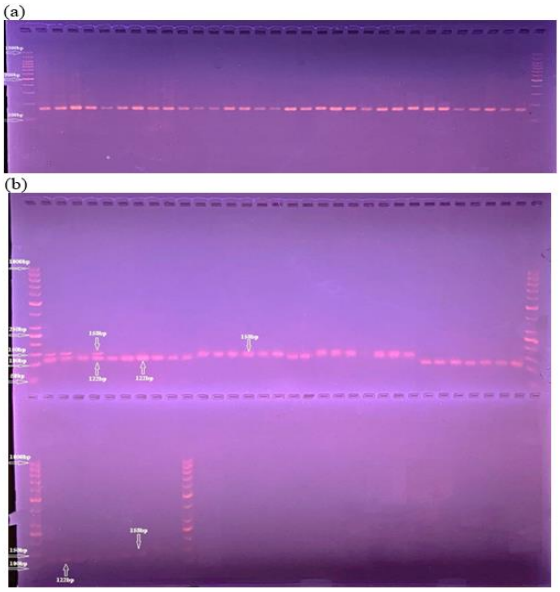

Figure 3: Molecular analysis of ABCC8 rs1801261 polymorphism using PCR and PCR-RFLP: a) agarose gel electrophoresis showing amplification of the ABCC8 rs1801261 fragment (158 bp); b) PCR-RFLP genotyping of ABCC8 rs1801261 after BsiEI digestion revealing CC (122 bp), TT (158 bp), and CT (158/122 bp) genotypes.

3.4 Genotype Frequencies and Associations with T1D

Table 2 presents genotype counts, odds ratios (OR), and 95% confidence intervals (CI) for each SNP comparing T1D patients to healthy. In ABCC8 rs1799854 SNP, the CT genotype showed a statistically significant predominance, with a threefold increase (95% CI 1.54-6.94) in T1D patients

compared to controls. Similarly, for KCNJ11 rs5219, CT genotype carriers had a significantly ~ 6-fold increased susceptibility for heterozygosity in diabetic patients ($p < 0.0001$). Regarding ABCC8 rs1801261 SNP, T1D patients carrying the TT genotype were associated with a protective effect against diabetes, showing 78% lower odds of disease compared to the CC genotype (OR = 0.22; 95% CI 0.08–0.63). However, the CT genotype of this same SNP didn't significantly differ between T1D and non-diabetic controls.

3.5 Correlations between Different Genotypes and Clinical Parameters in T1D

To evaluate the influence of specific SNP genotypes on different clinical and biochemical parameters in T1D patients, the association of different SNP genotypes with the different parameters was evaluated. Concerning ABCC8rs1799854 SNP, as shown in Table 3 and 4, both CC and CT genotypes were associated with significantly lower BMI in T1D patients compared to healthy individuals ($p=0.019$ and $p<0.001$, respectively). TC had noticeably lower levels in T1D carrying the CT genotype compared to healthy. HDL levels were significantly lower in T1D for both CC ($p=0.041$) and CT ($p=0.003$) carriers, whilst HbA1c and RBS were markedly elevated in T1D regardless of genotype (all $p<0.0001$). No significant genotype-based differences were observed in TG or TC.

Concerning ABCC8rs1801261 SNP, (Table 5) indicates a significantly lower BMI in CC and CT genotypes in T1D compared to healthy ($p= 0.037$ and $p= 0.003$, respectively). T1D CT carriers had significantly lower TC ($p<0.0001$), whilst CC carriers had lower HDL ($p<0.0001$) levels compared to controls. HbA1c and RBS were higher across all genotypes in T1D patients and controls ($p<0.0001$).

Furthermore, concerning KCNJ11rs5219 SNP, Table 6 illustrates that BMI was significantly lower in both CC and CT genotypes in T1D compared to healthy ($p=0.001$ and $p=0.022$). TC levels were significantly lower in T1D across both genotypes ($p<0.01$). HDL was significantly reduced in CT carriers ($p=0.018$), and HbA1c and RBS were significantly higher in T1D patients for both genotypes ($p<0.001$). However, TG and LDL levels did not differ significantly.

Table 3: SNP genotype frequencies and their relative risk in T1D patients compared with controls.

		Diabetes	Control	OR (95% CI)	p-value
ABCC8 rs1799854	CC	18	35	1	0.003*
	CT	42	25	3.3 (1.5-6.9)	
KCNJ11 rs5219	CC	14	39	1	<0.0001*
	CT	46	21	6.1(2.7-13.6)	
ABCC8 rs1801261	CC	17	27	1	0.013*
	CT	23	26	0.7 (0.3-1.6)	
	TT	20	7	0.2 (0.1-0.6)	

OR: odds ratio; 95% CI: 95% confidence interval, * p-value <0.05 is considered statistically significant.

Table 4: Comparison of clinical parameters by genotype for ABCC8rs1799854 SNP in T1D patients.

	Genotype	T1D	Control	p-value
BMI (kg/m²)	CC	17.21 ± 1.84	18.87 ± 3.12	0.019*
	CT	16.65 ± 2.26	19.32 ± 3.17	<0.001*
TG (mg/dL)	CC	120.77 ± 51.98	118.27 ± 31.17	0.853
	CT	130.74 ± 63.64	111.03 ± 36.46	0.112
TC (mg/dL)	CC	149.95 ± 40.53	164.70 ± 19.25	0.159
	CT	143.89 ± 56.57	178.80 ± 14.27	<0.0001*
HDL (mg/dL)	CC	43.73 ± 7.84	47.96 ± 6.49	0.041*
	CT	44.42 ± 9.30	50.21 ± 5.90	0.003*
LDL (mg/dL)	CC	117.66 ± 48.17	95.80 ± 18.04	0.078
	CT	94.88 ± 31.76	100.35 ± 18.87	0.38
HbA1c (%)	CC	10.17 ± 2.79	5.09 ± 0.56	<0.0001*
	CT	9.40 ± 2.17	4.97 ± 0.55	<0.0001*
RBS (mg/dL)	CC	306.65 ± 128.49	99.77 ± 13.98	<0.0001*
	CT	305.97 ± 142.10	98.96 ± 17.81	<0.0001*

* p-value <0.05 is considered statistically significant.

Table 5: Comparison of clinical parameters by genotype for ABCC8rs1801261 SNP in T1D patients.

	Genotype	T1D	Control	p-value
BMI (kg/m²)	CC	16.9 ± 2.3	18.8 ± 3.2	0.037*
	CT	17.0 ± 2.2	19.5 ± 3.1	0.003*
	TT	16.5 ± 2.1	18.4 ± 3.5	0.204
TG (mg/dL)	CC	148.3±78.1	113.3 ±31.4	0.094
	CT	105.0±43.9	112.1 ±33.1	0.522
	TT	136.5 ±52.6	134.5±40.2	0.928
TC (mg/dL)	CC	165.0± 62.3	169.5 ±22.3	0.779
	CT	130.5 ±47.4	175.4 ±13.3	<0.0001*
	TT	146.8 ±43.6	156.8 ±13.6	0.371
HDL (mg/dL)	CC	40.4 ± 8.7	49.3 ± 6.13	<0.0001*
	CT	48.6 ± 8.7	49.4 ± 6.1	0.693
	TT	42.5 ± 7.1	45.5± 7.6	0.356
LDL (mg/dL)	CC	101.0± 33.8	93.0± 20.6	0.388
	CT	92.8 ± 22.6	102.1 ±16.3	0.1
	TT	112.6± 53.1	99.5 ± 13.8	0.32
HbA1c (%)	CC	9.9 ± 2.2	5.1 ± 0.6	<0.0001*
	CT	8.7 ± 2.4	5.0± 0.6	<0.001*
	TT	10.5 ± 2.3	5.2 ± 0.5	<0.0001*
RBS (mg/dL)	CC	333.6±131.8	98.6 ± 16.9	<0.0001*
	CT	279.8±145.5	99.1 ± 15.9	<0.0001*
	TT	313.2±132.7	103.7± 8.4	<0.0001*

* p-value <0.05 is considered statistically significant.

Table 6: Comparison of clinical parameters by genotype for KCNJ11rs5219 SNP in T1D patients.

	Genotype	T1D	Control	p-value
BMI (kg/m²)	CC	16.00 ± 2.48	19.11 ± 3.08	0.001*
	CT	17.06 ± 1.99	18.95 ± 3.28	0.022*
TG (mg/dL)	CC	144.93 ± 65.58	113.80 ± 35.93	0.111
	CT	122.52 ± 58.10	117.95 ± 28.63	0.668
TC (mg/dL)	CC	138.50 ± 37.92	170.07 ± 19.45	0.009*
	CT	147.91 ± 55.77	171.50 ± 17.29	0.011*
HDL (mg/dL)	CC	42.49 ± 10.10	48.44 ± 6.30	0.055
	CT	44.73 ± 8.45	49.76 ± 6.36	0.018*
LDL (mg/dL)	CC	85.04 ± 29.38	97.92 ± 19.85	0.146
	CT	106.79 ± 39.73	97.28 ± 15.71	0.166
HbA1c (%)	CC	9.15 ± 1.73	+5.01 ± 0.55	<0.001*
	CT	9.78 ± 2.53	5.10 ± 0.57	<0.001*
RBS (mg/dL)	CC	289.33 ± 133.35	99.56 ± 16.99	<0.001*
	CT	311.30 ± 139.22	99.19 ± 12.85	<0.001*

* p-value <0.05 is considered statistically significant.

Table 7: Hardy–weinberg equilibrium test for ABCC8 (rs1799854, rs1801261) and KCNJ11 (rs5219) polymorphisms in T1D patients and controls.

		CC		CT		TT		χ^2	p-value
		Observed	Expected	Observed	Expected	Observed	Expected		
ABCC8 rs179985	T1D	18	25.35	42	27.3	0	7.35	17.39	<0.0001*
	Control	35	37.66	25	19.8	0	2.6	4.18	0.041*
ABCC8 rs1801261	T1D	17	13.54	23	29.93	20	16.53	3.22	0.07
	Control	27	26.69	26	26.66	7	6.67	0.04	0.846
KCNJ11 rs5219	T1D	14	22.8	46	28.3	0	8.8	23.18	<0.0001*
	Control	39	40.9	21	17.3	0	1.8	2.7	0.1

*(p-value <0.05) is considered statistically significant).

3.6 Hardy-Weinberg Equilibrium of ABCC8 and KCNJ11 Genotype

To verify that our genotype distributions conformed to expectations and to rule out population stratification, we performed Hardy–Weinberg equilibrium (HWE) analysis for each SNP separately in the T1D and control groups using a Chi-squared test. Observed genotype counts were compared to those expected under HWE, and p-values > 0.05 would indicate no significant deviation. As shown in Table 7, in the control group, ABCC8 rs1801261 ($\chi^2 = 0.04$, $p = 0.846$) and KCNJ11 rs5219 ($\chi^2 = 2.70$, $p = 0.10$) both conformed to expected genotype frequencies, indicating reliable genotyping and minimal population stratification. By contrast, ABCC8 rs1799854 showed a deviation in controls ($\chi^2 = 4.18$, $p = 0.041$), whilst among T1D patients, ABCC8 rs179985 ($\chi^2 = 17.39$, $p < 0.0001$) and KCNJ11 rs5219 ($\chi^2 = 23.18$, $p < 0.0001$) both deviated markedly from equilibrium, consistent with their significant disease associations, whilst ABCC8 rs1801261 remained in equilibrium ($\chi^2 = 3.22$, $p = 0.07$).

4 DISCUSSION

This study demonstrates a significant association between polymorphisms in ABCC8 (rs1799854, rs1801261) and KCNJ11 (rs5219) and susceptibility to type 1 diabetes (T1D) in children from Al-Muthanna Province, Iraq. Notable differences in genotype distributions were observed between T1D patients and healthy controls, alongside significant genotype-related variations in metabolic parameters.

The ABCC8 rs1799854 CT genotype was associated with an increased risk of T1D (OR = 3.27), while the rs1801261 TT genotype appeared to confer a protective effect (OR = 0.22). For KCNJ11 rs5219, the CT genotype showed the strongest association with disease susceptibility (OR ≈ 6.1), suggesting a potential role in modulating β-cell function and insulin secretion.

Furthermore, risk-associated genotypes were linked to an adverse metabolic profile characterized by lower BMI and HDL levels and higher HbA1c and random blood glucose, indicating a possible influence of these variants on glycemic control beyond disease susceptibility.

Although previous studies have primarily focused on these variants in type 2 diabetes, our findings suggest that KATP channel gene polymorphisms may also contribute to T1D pathophysiology in a pediatric population. However, inconsistencies with some genome-wide association studies highlight the possibility of population-specific effects or linkage disequilibrium rather than direct causality.

Deviations from Hardy–Weinberg equilibrium observed in patient groups further support a disease association, although these results should be interpreted cautiously due to potential sample size limitations and population stratification.

5 CONCLUSIONS

In conclusion, this study provides evidence that polymorphisms in the KATP channel genes, specifically ABCC8 (rs1799854 and rs1801261) and KCNJ11 (rs5219), are significantly associated with susceptibility to type 1 diabetes (T1D) in a pediatric population from Al-Muthanna Province, Iraq. The observed genotype distributions suggest that certain variants, particularly the ABCC8 rs1799854 CT genotype and KCNJ11 rs5219 CT genotype, may increase the risk of developing T1D, whereas the ABCC8 rs1801261 TT genotype may exert a protective effect.

Beyond disease susceptibility, these genetic variants were also associated with clinically relevant metabolic differences. Carriers of risk genotypes exhibited poorer glycemic control, reflected by elevated HbA1c and random blood glucose levels, as well as unfavorable lipid profiles characterized by reduced HDL levels. These findings indicate that ABCC8 and KCNJ11 polymorphisms may contribute not only to disease risk but also to inter-individual variability in metabolic control among children with T1D.

From a mechanistic perspective, the results support the biological plausibility that alterations in KATP channel subunits can influence pancreatic β-cell excitability and insulin secretion dynamics, thereby contributing to dysglycemia and disease progression. However, the inconsistencies with some previously published genome-wide association studies suggest that these effects may be population-specific or influenced by linkage disequilibrium with other functional variants.

Despite these important findings, the study is limited by its relatively small sample size and single-center design, which may affect statistical power and generalizability. In addition, potential population stratification cannot be fully excluded.

Therefore, larger multi-center and ethnically diverse studies are required to confirm these

associations and clarify the functional role of ABCC8 and KCNJ11 variants in T1D pathogenesis. If validated, these genetic markers could contribute to early risk stratification, improved understanding of disease heterogeneity, and potentially personalized approaches to the management of pediatric T1D.

ACKNOWLEDGMENTS

We are grateful to all patients who participated in this study for their kind cooperation, and we extend our gratitude to Al-Hussein Teaching Hospital, Department of Diabetes and Endocrinology, for their valuable support in data collection and clinical assistance.

REFERENCES

[1] A. Zajec, K. Trebušak Podkrajšek, T. Tesovnik, R. Šket, B. Čugalj Kern, B. Jenko Bizjan, et al., "Pathogenesis of Type 1 Diabetes: Established Facts and New Insights," Genes (Basel), vol. 13, no. 4, Apr. 2022, [Online]. Available: https://doi.org/10.3390/genes13040706.

[2] M. Von Herrath, S. Sanda, and K. Herold, "Type 1 diabetes as a relapsing-remitting disease?," Nature Reviews Immunology, vol. 7, no. 12, pp. 988-994, 2007.

[3] R. A. Insel, J. L. Dunne, M. A. Atkinson, J. L. Chiang, D. Dabelea, P. A. Gottlieb, et al., "Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association," Diabetes Care, vol. 38, no. 10, pp. 1964-1974, 2015, [Online]. Available: https://doi.org/10.2337/dc15-1419.

[4] D. Dabelea, R. A. Bell, R. B. D'Agostino Jr, G. Imperatore, J. M. Johansen, B. Linder, et al., "Incidence of diabetes in youth in the United States," JAMA, vol. 297, no. 24, pp. 2716-2724, 2007.

[5] G. Stipancic, M. P. Sepec, L. L. Sabolic, A. Radica, V. Skrabic, S. Severinski, et al., "Clinical characteristics at presentation of type 1 diabetes mellitus in children younger than 15 years in Croatia," J. Pediatr. Endocrinol. Metab., vol. 24, no. 9-10, pp. 665-670, 2011, [Online]. Available: https://doi.org/10.1515/jpem.2011.231.

[6] E. F. Roche, A. M. McKenna, M. O'Regan, K. J. Ryder, H. M. Fitzgerald, and H. Hoey, "The incidence of type 1 diabetes in children under 15 years of age is rising again-a nationwide study," Eur. J. Pediatr., vol. 182, no. 10, pp. 4615-4623, 2023, [Online]. Available: https://doi.org/10.1007/s00431-023-05125-.

[7] M. J. Redondo, A. K. Steck, and A. Pugliese, "Genetics of type 1 diabetes," Pediatr. Diabetes, vol. 19, no. 3, pp. 346-353, 2018.

[8] M. Klak, M. Gomółka, P. Kowalska, J. Cichoń, F. Ambrożkiewicz, M. Serwańska-Świętek, et al., "Type 1 diabetes: genes associated with disease development," Cent. Eur. J. Immunol., vol. 45, no. 4, pp. 439-453, 2020, [Online]. Available: https://doi.org/10.5114/ceji.2020.103386.

[9] P. Haghvirdizadeh, Z. Mohamed, N. A. Abdullah, P. Haghvirdizadeh, M. S. Haerian, and B. S. Haerian, "KCNJ11: Genetic polymorphisms and risk of diabetes mellitus," J. Diabetes Res., vol. 2015, p. 908152, 2015, [Online]. Available: https://doi.org/10.1155/2015/908152.

[10] P. Haghverdizadeh, M. Sadat Haerian, P. Haghverdizadeh, and B. Sadat Haerian, "ABCC8 genetic variants and risk of diabetes mellitus," Gene, vol. 545, no. 2, pp. 198-204, 2014, [Online]. Available: https://doi.org/10.1016/j.gene.2014.04.040.

[11] F. M. Ashcroft, "ATP-sensitive potassium channelopathies: focus on insulin secretion," J. Clin. Invest., vol. 115, no. 8, pp. 2047-2058, 2005, [Online]. Available: https://doi.org/10.1172/jci25495.

[12] S. Reddy, S. Maddhuri, P. Nallari, V. Ananthapur, S. Kalyani, M. Krishna, et al., "Association of ABCC8 and KCNJ11 gene variants with type 1 diabetes in south Indians," Egypt. J. Med. Hum. Genet., vol. 22, no. 1, p. 27, 2021, [Online]. Available: https://doi.org/10.1186/s43042-021-00149-w.

[13] N. A. ElSayed, R. G. McCoy, G. Aleppo, K. Balapattabi, E. A. Beverly, K. Briggs Early, et al., "Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2025," Diabetes Care, vol. 48, 2025.

[14] M. Q. Waheeb, Y. A. Jabbar Alabdali, and H. A. Azez, "Gene Polymorphism Vitamin D receptor BsmI in Thalassemia Children in Al-Muthanna Province," Indian J. Forensic Med. Toxicol., vol. 14, no. 3, 2020.

[15] M. Q. Waheeb, H. A. Aziz, and Y. A. J. Alabdali, "Gene polymorphism vitamin D receptor FokI in thalassemia children in AL-Muthanna province," Medico-Legal Update, vol. 19, no. 2, pp. 383-389, 2019.

[16] D. Bodhini and V. Mohan, "Diabetes Burden in the IDF-MENA Region," J. Diabetol., vol. 13, Suppl. 1, pp. S1-S2, 2022, [Online]. Available: https://doi.org/10.4103/jod.jod_125_22.

[17] A. R. O. Jasim, N. A. Razzaq, A. T. A. Imeer, R. M. Rahem, A. A. H. Kadhum, and A. A. Al-Amiery, "Epidemiological profile and diabetes control of Type 1 Diabetes Mellitus patients in Karbala Governorate, Iraq," F1000Research, vol. 12, p. 409, 2023.

[18] D. Almahfoodh, M. Alabbood, A. Alali, and A. Mansour, "Epidemiology of type 1 diabetes mellitus in Basrah, Southern Iraq: A retrospective study," Diabetes Res. Clin. Pract., vol. 133, pp. 104-108, 2017, [Online]. Available: https://doi.org/10.1016/j.diabres.2017.09.001.

[19] D. M. Maahs, N. A. West, J. M. Lawrence, and E. J. Mayer-Davis, "Epidemiology of type 1 diabetes," Endocrinol. Metab. Clin. North Am., vol. 39, no. 3, pp. 481-497, 2010, [Online]. Available: https://doi.org/10.1016/j.ecl.2010.05.011.

[20] S. H. Zalzala, F. H. Al-Lami, and K. S. Fahad, "Epidemiological profile of type 1 diabetes among primary school children in Baghdad, Iraq," J. Contemp. Med. Sci., vol. 6, no. 1, 2020.

[21] I. Hormazábal-Aguayo, Y. Ezzatvar, N. Huerta-Uribe, R. Ramírez-Vélez, M. Izquierdo, and

A. García-Hermoso, "Incidence of type 1 diabetes mellitus in children and adolescents under 20 years of age across 55 countries from 2000 to 2022: A systematic review with meta-analysis," Diabetes/Metab. Res. Rev., vol. 40, no. 3, p. e3749, 2024.

[22] L. A. Albishi, M. M. Altoonisi, S. M. Alblewi, R. H. Osman, N. A. Ahmed, and M. Fararjeh, "Clinical demographic patterns of type 1 diabetes in Saudi children in Tabuk City, 2000-2010," J. Diabetes Mellitus, vol. 7, no. 2, p. 41, 2017.

[23] A. A. Shaltout, D. Wake, T. A. Thanaraj, D. M. Omar, D. Al-AbdulRazzaq, A. Channanath, et al., "Incidence of type 1 diabetes has doubled in Kuwaiti children 0-14 years over the last 20 years," Pediatr. Diabetes, vol. 18, no. 8, pp. 761-766, 2017.

[24] M. Sidell, M. P. Martinez, T. Chow, and A. H. Xiang, "Types of diabetes during pregnancy and longitudinal BMI in offspring from birth to age 10 years," Pediatr. Obes., vol. 16, no. 8, p. e12776, 2021.

[25] N. L. Davis, J. D. Bursell, W. D. Evans, J. T. Warner, and J. W. Gregory, "Body composition in children with type 1 diabetes in the first year after diagnosis: relationship to glycaemic control and cardiovascular risk," Arch. Dis. Child., vol. 97, no. 4, pp. 312-315, 2012.

[26] M. Lestari, I. Faridah, R. Maliza, H. Dania, M. Widianingrum, and D. Perwitasari, "Identification of SNP rs1799854 ABCC8 gene and blood glucose levels in patients with type 2 diabetes mellitus at Moewardi hospital Surakarta Solo," Pharmaciana, vol. 11, pp. 338-346, 2021, [Online]. Available: https://doi.org/10.12928/pharmaciana.v11i3.19100.

[27] X. Zhou, C. Chen, D. Yin, F. Zhao, Z. Bao, Y. Zhao, et al., "A variation in the ABCC8 gene is associated with type 2 diabetes mellitus and repaglinide efficacy in Chinese type 2 diabetes mellitus patients," Intern. Med., vol. 58, no. 16, pp. 2341-2347, 2019.

[28] F. M. Ashcroft, "KATP Channels and the Metabolic Regulation of Insulin Secretion in Health and Disease: The 2022 Banting Medal for Scientific Achievement Award Lecture," Diabetes, vol. 72, no. 6, pp. 693-702, 2023, [Online]. Available: https://doi.org/10.2337/dbi22-0030.

[29] S. M. Raj, J. M. M. Howson, N. M. Walker, J. D. Cooper, D. J. Smyth, S. F. Field, et al., "No association of multiple type 2 diabetes loci with type 1 diabetes," Diabetologia, vol. 52, no. 10, pp. 2109-2116, 200.