




# SLC22A1 And ATM Genes Polymorphisms Are Associated With The Risk Of Type 2 Diabetes Mellitus In Western Saudi Arabia: A Case-Control Study

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**Introduction:** Type 2 diabetes mellitus (T2DM) is a major global health problem that is progressively affected by genetic and environmental factors. The aim of this study is to determine the influence of solute carrier family 22 member 1 (*SLC22A1*) rs628031 and rs461473, and ataxia telangiectasia mutated (*ATM*) rs11212617 polymorphisms on the risk of T2DM in Saudi Arabia by considering many parameters associated with glycemic control of T2DM, such as body mass index (BMI), fasting blood glucose, glycated hemoglobin (HbA1c), and triglyceride.

**Methods:** In a case-control study, genomic DNA from controls and diabetic groups was isolated and genotyped for each single-nucleotide polymorphism.

**Results:** There were significant correlations between T2DM and both BMI and HbA1c. Significant associations between G/G and A/G genotypes of rs628031 and rs461473 variants of *SLC22A1* and high levels of HbA1c were detected. Therefore, G was predicted to be the risk allele among the assessed *SLC22A1* variants. A significant correlation was observed between A/A and A/C genotypes of the rs11212617 polymorphism of *ATM* and elevated HbA1c. Relative risk calculation confirmed A to be the risk allele in the T2DM population.

**Conclusion:** Our study showed the risk of the assessed *SLC22A1* and *ATM* variants on glycemic control parameters in diabetic patients.

**Keywords:** type 2 diabetes mellitus, single-nucleotide polymorphism, solute carrier family 22 member 1, ataxia telangiectasia mutated

## Introduction

Type 2 diabetes mellitus (T2DM) is a major chronic disease that is affected by genetic and environmental factors.<sup>1,2</sup> The International Diabetic Federation estimated that there were approximately 4.0 million cases of diabetes in Saudi Arabia in 2017.<sup>3</sup> Saudi Arabia is ranked fourth in the Middle East/North Africa region in diabetes prevalence.<sup>3</sup> Risk factors for T2DM are particularly prevalent among the Saudi Arabian population due to an increase in metabolic syndrome, physical inactivity, obesity, cigarette smoking, and poor dietary habits.<sup>4</sup>

Establishment of single-nucleotide polymorphism (SNP) databases, development and improvement of cost-effective high-throughput genotyping technology, and multi-center consortium large-scale genome-wide association studies (GWAS) are effective methods to investigate genetic susceptibility to T2DM. By searching susceptibility

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variants across the entire genome in an unbiased, hypothesis-free manner, GWAS have successfully identified genetic *loci* strongly related to T2DM, the number of which has risen from just three in 2006 to approximately 70 today.<sup>5</sup> The first GWAS research for T2DM was performed on a European cohort in 2007. This analysis identified many novel susceptibility genes associated with T2DM.<sup>6</sup> However, studies of European ancestry comprise only a subset of human genetic variation and are considered inadequate to fully characterize T2DM risk variants in other ethnic groups. Furthermore, the latest genome-wide genotyping arrays are less biased toward Europeans, and more recent T2DM GWAS have been performed with great success in populations from other ancestry groups, including South Asians, East Asians, Mexicans, Mexican-Americans, and African-Americans.<sup>7</sup>

Studies of classic genetic screens have taught us that some candidate genes can indirectly affect the glycemic response, for example, variations in the solute carrier family 22 member 1 (*SLC22A1*) gene influence the rate of control of T2DM, rather than any major signaling pathway.<sup>8</sup> The human *SLC22A1* gene is located on chromosome 6q25.3 and encodes for organic cation transporter 1 (OCT1); it consists of 11 exons spanning 37 kb and has been shown to play an important role in the control of the glycemic response of T2DM.<sup>9</sup> Population studies have shown a high level of polymorphisms for *SLC22A1* in different ethnicities.<sup>10,11</sup>

Association of the polymorphism rs628031 (M408V) with the glycemic response has been assessed in many studies. It is the most common-genotyped variant with a frequency of 15% to 80% (median, 36%).<sup>12</sup> The Japanese population has the highest frequency (80%)<sup>13</sup> while rs628031 is present in only 40% of Caucasians.<sup>14</sup> Another *SLC22A1* variant, rs461473, has not been sufficiently studied. In the Jordanian population, the minor allele frequency was calculated in diabetic subjects (A = 10%) but no significant association between this SNP and glycemic control was detected.<sup>15</sup>

Mutations in the ataxia telangiectasia mutated (*ATM*) gene were proposed to have a causative role in ataxia telangiectasia, an autosomal recessive disorder with manifestations including insulin resistance and T2DM.<sup>8</sup> A novel variant of the *ATM* gene (rs11212617) was shown to strongly affect glycemic control in T2DM patients.<sup>8</sup> The discovery of the role of *ATM* polymorphism in the risk of T2DM modulating glycemic response might provide a clue to the treatment mechanism of this disease.<sup>16</sup> The *ATM* gene contributes to DNA repair, cell cycle control and also plays a role in the

adenosine monophosphate activation of protein kinase that affects glycemic control of T2DM.<sup>17</sup> A 150 kb gene on chromosome 11q22-23, *ATM* contains 66 exons encoding a 13 kb transcript.<sup>9</sup> A previous UK study showed a frequency of 44% for the C allele of the rs11212617 A>C SNP in the *ATM* gene, and reported that the C allele was associated with an HbA1c level of less than 7%.<sup>17</sup> A significant association between the C allele of rs11212617 and HbA1c level in a cohort of Han Chinese diabetes mellitus patients was detected in Shanghai.<sup>18</sup>

Of great importance in the genetic studies of the pathogenesis of T2DM are the clinical parameters such as reduction of HbA1c, fasting blood glucose (FBS), and postprandial plasma glucose.<sup>19</sup> The genotype distribution and allele frequencies of different variants related to glycemic control vary among different populations.<sup>14,20</sup> Therefore, the aim of this study is to determine the genotype and allele frequencies of the genetic variants of *SLC22A1* (rs628031 and rs461473) and *ATM* (rs11212617) and detect their association with T2DM risk in western Saudi Arabia.

## Materials And Methods

### Study Design

The inclusion criteria for this case-control study of 201 T2DM patients were: age >37 years, HbA1c <10%, and under current treatment with metformin and/or other T2DM drugs. Patients with other chronic diseases including cardiovascular disease and metabolic syndrome were excluded. The results from T2DM patients were compared with 89 non-diabetic healthy controls. Patients and controls were recruited either from King Abdulaziz University Hospital or Jeddah Care Center for Diabetes and Hypertension in Jeddah, Saudi Arabia between 2016 and 2018. The study was approved by the Biomedical Ethics Unit, Faculty of Medicine, King Abdulaziz University (approval number 371-16) and Ministry of Health (approval number A00363) and written informed consent was obtained from participants prior to sample collection. The study was conducted in accordance with the Declaration of Helsinki. All participants' clinical parameters were recorded: age, sex, body weight, height, body mass index (BMI), HbA1c level, FBS, and lipid profile (Table 1). Most patients had a family history of diabetes.

### Genotyping

Genomic DNA was isolated from peripheral whole blood using the QIAamp DNA Mini Blood Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions.

**Table 1** Clinical Characteristics Of Diabetic And Control Subjects

Variable	Diabetic Sample (n = 201)	Control Sample (n = 89)	p-value
Age (years)	60 ± 11.5	48 ± 11.5	≤0.001
Gender, M/F	78/118	56/33	≤0.001
BMI (kg/m <sup>2</sup> )	29.3 ± 5.9	27 ± 6.0	0.004
FBS (mmol/L)	8.6±3.6	5.5±1.0	≤0.001
HbA1c (%)	8 ± 1.6	5.6 ± 0.43	≤0.001
Triglycerides (mmol/L)	1.1 ± 0.76	0.7 ± 0.5	≤0.001
Cholesterol (mmol/L)	4.7 ± 1.16	4.6 ± 1.1	0.807

**Notes:** Values are expressed as mean±SD, p-values were calculated by Student's t-test. p-value <0.05 is statistically significant.

**Abbreviations:** BMI, body mass index; FBS, fasting blood glucose; HbA1c, glycated hemoglobin test.

Genotyping of the *SLC22A1* variants rs628031 (assay ID: C\_8709275\_60), rs461473 (assay ID: C\_928539\_10), and *ATM* variant rs11212617 (assay ID: C\_1314213\_10) was performed using TaqMan™ SNP Genotyping Assays (Thermo Fisher Scientific, Waltham, MA, USA). Allelic polymerase chain reaction (PCR) products were analyzed using QuantStudio 12K Flex Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA).

## Statistical Analysis

Data analysis was conducted using the IBM SPSS Statistics software, Version 24 (IBM Corp., Armonk, NY, USA). Genotypes and allelic frequencies were calculated within our cohort population to determine the significant differences between T2DM patients and control groups. A binary logistic regression unadjusted model was used to study the association between variables and the study groups. Odds ratios (ORs) were calculated to determine the risk of many variables and development of T2DM using the logistic regression test. For all correlations,  $p < 0.05$  was considered statistically significant.

## Results

### Allele And Genotype Frequency

The allele frequencies and genotype distributions of *SLC22A1* rs461473, rs628031, and *ATM* rs11212617 are listed in Table 2.

### The Association Between Multiple Factors And T2DM

The results revealed strong significant association between T2DM and BMI (OR = 1.072,  $p = 0.005$ ), FBS (OR = 2.715,  $p < 0.001$ ), HbA1c (OR = 52.647,  $p < 0.001$ ), and triglycerides (OR = 1.013,  $p < 0.001$ ) but not with the other variables using unadjusted binary logistic regression.

### The Association Of *SLC22A1* Variants Rs628031 And Rs461473 And *ATM* Variant Rs11212617 With Clinical Parameters For T2DM Patients

The impact of BMI, FBS, HbA1c, and triglycerides on T2DM in the presence of *SLC22A1* and *ATM* variants was determined using binary logistic regression. There was a significant association between BMI and the genotype G/G of *SLC22A1* SNP rs628031 (OR = 1.13,  $p = 0.003$ ). In addition, significant elevation in FBS was more likely associated with G/G and A/G genotypes of *SLC22A1* rs628031 (OR = 4.060,  $p < 0.001$ ; OR = 3.260,  $p < 0.001$ ). We also found a significant correlation between G/G and A/G genotypes with HbA1c (OR = 156.924,  $p < 0.001$  and OR = 65.6,  $p < 0.001$ , respectively); the patients with G/G and A/G are more likely to have a high level of HbA1c than patients with A/A in the rs628031 variant. In addition, G/G and A/G genotypes were correlated with an increase in triglycerides (OR = 1.019,  $p = 0.001$  and OR = 1.01,  $p = 0.027$ , respectively). Hence, the G allele in rs628031 is potentially a risk

**Table 2** Genotype And Allele Frequencies For *SLC22A1* Variants Rs628031 And Rs461473, And *ATM* Rs11212617

SNP	<i>SLC22A1</i> rs628031			<i>SLC22A1</i> rs461473			<i>ATM</i> rs11212617		
	A/A	A/G	G/G	A/A	A/G	G/G	A/A	A/C	C/C
Genotype frequency									
DM (n = 201)	21 (11.5%)	69 (38%)	92 (50.5%)	2 (1%)	44 (23.2%)	144 (75.8%)	97 (49.2%)	73 (37.1%)	27 (13.7%)
Control (n = 89)	7 (7.9%)	38 (42.7%)	44 (49.4%)	0 (0%)	12 (13.5%)	77 (86.5%)	34 (38.2%)	36 (40.4%)	19 (21.4%)
Allele frequency	A		G	A		G	A		C
DM	111 (30.5%)		253 (69.5%)	48 (12.6%)		332 (87.4%)	267 (67.8%)		127 (32.2%)
Control	52 (29.2%)		126 (70.8%)	12 (6.7%)		166 (93.3%)	104 (58.4%)		74 (41.6%)

**Abbreviations:** SNP, single-nucleotide polymorphisms; *SLC22A1*, solute carrier family 22 member 1; DM, diabetes mellitus; *ATM*, ataxia telangiectasia mutated.

allele associated with high BMI, FBS, HbA1c, and triglycerides in T2DM (summarized in Table 3).

Our results showed a significant association between BMI and the genotype G/G of *SLC22A1* rs461473 (OR = 1.107,  $p = 0.001$ ). In addition, patients with G/G and A/G genotypes of *SLC22A1* rs461473 were more likely to have high levels of FBS (OR = 2.543,  $p < 0.001$  and OR = 14.231,  $p = 0.008$ , respectively). There was a significant correlation between G/G and A/G genotypes with HbA1c (OR = 64.124,  $p < 0.001$  and OR = 31.055,  $p = 0.004$ , respectively). Therefore, the patients with G/G and A/G are more likely to have greater HbA1c than patients with A/A in rs461473. Furthermore, G/G and A/G genotypes correlated with an increase in triglycerides (OR = 1.013,  $p < 0.001$  and OR = 1.028,  $p = 0.035$ , respectively). Thus, the G allele in rs461473 is potentially a risk allele associated with high BMI, FBS, HbA1c, and triglycerides in T2DM (summarized in Table 4).

In *ATM* variant rs11212617, there was a significant association between FBS and the genotypes A/A (OR = 5.369,  $p < 0.001$ ) and A/C (OR = 3.059,  $p < 0.001$ ). In addition, a significant positive correlation between A/A and A/C genotypes and HbA1c was detected (OR = 62.239,  $p < 0.001$  and OR = 83.349,  $p < 0.001$ , respectively, Table 5). To confirm the risk allele, the relative risk was calculated to define A as the risk allele highly correlated to T2DM 1.137 times more than the control group.

## Discussion

T2DM is a complex metabolic disease with an increasing prevalence particularly over the past two decades,<sup>4</sup> in which both genetic determinants and environmental factors play important roles.<sup>21</sup> The glycemic control of T2DM varies widely from person to person; research has shown that more than one-third of T2DM patients do not achieve appropriate control of fasting glucose levels.<sup>16</sup> The major cause of the uncontrolled glycemic levels of these patients is genetic variation.<sup>9,22</sup> The candidate gene approach for conducting genetic association studies focuses on relations between genetic variation within prespecified genes of interest and phenotypes or disease states. Various susceptibility genes for T2DM have recently been identified for several populations through GWAS.<sup>4</sup>

Studies have largely used genotyping technology with moderate sample sizes to find genetic variants related to T2DM risk.<sup>21</sup> Case-control studies are often used to find differences in the allele frequency of a candidate gene among case and control subjects.<sup>23,24</sup> Research has shown that the *SLC22A1* and *ATM* genes play an important role in glycemic control in T2DM patients.<sup>2,25–27</sup> Most studies have used HbA1c as a surrogate marker for glycemic response and association of candidate genes variants with the risk of T2DM.<sup>9</sup> In this study, we showed an association between *SLC22A1* and *ATM* variants and the risk of T2DM in Saudi subjects, and investigated the effect

**Table 3** The Association Of *SLC22A1* Variant Rs628031 With T2DM Phenotypes Using Binary Logistic Regression For Patients In Regard To Controls

Genotype <i>SLC22A1</i> rs628031	Factors	B	p-value	OR	95% CI For OR	
					Lower	Upper
A/A	BMI (kg/m <sup>2</sup> )	0.148	0.124	1.16	0.96	1.401
	FBS (mmol/L)	1.280	0.093	3.595	0.806	16.034
	HbA1c (%)	3.152	0.022	23.392	1.574	347.614
	Triglycerides (mmol/L)	0.055	0.067	1.057	0.996	1.121
A/G	BMI (kg/m <sup>2</sup> )	0.014	0.669	1.014	0.952	1.08
	FBS (mmol/L)	1.182	<0.001	3.260	1.824	5.825
	HbA1c (%)	4.184	<0.001	65.616	10.145	424.414
	Triglycerides (mmol/L)	0.01	0.027	1.010	1.001	1.019
G/G	BMI (kg/m <sup>2</sup> )	0.122	0.003	1.13	1.043	1.225
	FBS (mmol/L)	1.401	<0.001	4.060	2.347	7.023
	HbA1c (%)	5.056	<0.001	156.924	17.792	1384.059
	Triglycerides (mmol/L)	0.018	0.001	1.019	1.007	1.03

**Note:** The p-value was calculated by binary logistic regression.

**Abbreviations:** BMI, body mass index; HbA1c, glycated hemoglobin test; OR, odds ratio; CI, confidence intervals.

**Table 4** The Association Of *SLC22A1* Variant Rs461473 With T2DM Phenotypes Using Binary Logistic Regression For Patients In Regard To Controls

Genotype <i>SLC22A1</i> rs461473	Factors	B	p-value	OR	95% CI For OR	
					Lower	Upper
A/G	BMI (kg/m <sup>2</sup> )	-0.044	0.416	0.957	0.86	1.064
	FBS (mmol/L)	2.655	0.008	14.231	2.016	100.430
	HbA1c (%)	3.436	0.004	31.055	3.043	316.96
	Triglycerides (mmol/L)	0.027	0.035	1.028	1.002	1.054
G/G	BMI (kg/m <sup>2</sup> )	0.101	0.001	1.107	1.044	1.172
	FBS (mmol/L)	0.933	<0.001	2.543	1.857	3.482
	HbA1c (%)	4.161	<0.001	64.124	18.226	225.602
	Triglycerides (mmol/L)	0.013	<0.001	1.013	1.006	1.020

**Note:** The p-value was calculated by binary logistic regression.

**Abbreviations:** BMI, body mass index; HbA1c, glycated hemoglobin test; OR, odds ratio; CI, confidence intervals.

of the genotypes on BMI, FBS, HbA1c, triglycerides, and other factors for T2DM patients.

Several studies have reported a positive association between *SLC22A1* variants and T2DM risk<sup>28</sup> among Asian, European, and Caucasian populations.<sup>12</sup> The common polymorphism of *SLC22A1*, rs628031 (A>G) causes a missense variant with variable frequencies in different ethnic populations. This polymorphism tends to lower *SLC22A1* mRNA expression in enterocytes leading to decreased intestinal uptake and subsequent accumulation of drugs.<sup>29</sup> No significant effects of this polymorphism against glycemic response have been detected in Iranians,<sup>9</sup> Indians,<sup>30</sup> or Japanese populations.<sup>13,31</sup> In our study, the

frequency of the G allele in rs628031 was 69.5%, similar to other populations such as Koreans (74%),<sup>32</sup> Asians living in the USA (76.2%), and African-Americans (73.5%).<sup>33</sup> The frequency was slightly lower in European Caucasians (59.8%),<sup>33</sup> in Germany (57.4%),<sup>34</sup> and in the Netherlands.<sup>14</sup> In Han Chinese, the G/G genotype of rs628031 correlated to a significant reduction in fasting plasma glucose and higher levels of HbA1c, whereas the A/A genotype was associated with a significant reduction in HbA1c,<sup>18</sup> and a positive predictor of treatment efficacy in the Japanese population.<sup>31</sup> Similarly, in the present study, we showed that the G allele in the rs628031 variant is the risk allele, and patients with the G/G genotype have higher levels of HbA1c and FBS

**Table 5** The Correlation Of *ATM* Variant Rs11212617 With T2DM Phenotypes Using Binary Logistic Regression For Patients In Regard To Controls

Genotype <i>ATM</i> rs11212617	Factors	B	p-value	OR	95% CI For OR	
					Lower	Upper
A/A	BMI (kg/m <sup>2</sup> )	0.075	0.056	1.078	0.998	1.165
	FBS (mmol/L)	1.681	<0.001	5.369	2.474	11.652
	HbA1c (%)	4.131	<0.001	62.239	10.929	354.46
	Triglycerides (mmol/L)	0.008	0.060	1.008	1.000	1.016
A/C	BMI (kg/m <sup>2</sup> )	0.077	0.05	1.08	1.001	1.166
	FBS (mmol/L)	1.118	<0.001	3.059	1.826	5.124
	HbA1c (%)	4.423	<0.001	83.349	12.58	552.224
	Triglycerides (mmol/L)	0.017	0.004	1.017	1.006	1.029
C/C	BMI (kg/m <sup>2</sup> )	0.008	0.899	1.008	0.894	1.137
	FBS (mmol/L)	1.397	0.015	4.043	1.316	12.419
	HbA1c (%)	2.803	0.004	16.493	2.413	112.745
	Triglycerides (mmol/L)	0.23	0.028	1.024	1.003	1.045

**Note:** The p-value was calculated by binary logistic regression.

**Abbreviations:** BMI, body mass index; HbA1c, glycated hemoglobin test; OR, odds ratio; CI, confidence intervals.



than those with A/G and A/A genotypes. Reduced-function polymorphisms of OCT1 were significantly associated with high levels of cholesterol, triglycerides, and low-density lipoprotein. An Oct1 knockout mice model showed loss of function of OCT1 through decreased thiamine uptake in the liver that leads to reduced levels of thiamine pyrophosphate activity causing disruption in the fatty acid oxidation pathway.<sup>35</sup> This could explain our genetic finding that OCT1 variants are potentially a genetic risk factor associated with high triglyceride levels in T2DM.

An intronic variant rs461473 in *SLC22A1* was also found to be associated with a decrease in HbA1c and glucose lowering after initiation of treatment.<sup>36</sup> This finding is compatible with our results as we found a link between the G allele in the *SLC22A1* rs461473 variant and raised levels of HbA1c. In contrast, other studies found no significant relationship between the variant and the glycemic control of T2DM patients in Dutch,<sup>14</sup> Japanese,<sup>31</sup> or Jordanian populations.<sup>15</sup>

The role of *ATM* gene variant rs1121617 in the etiology of diabetes was assessed by comparing the allele and genotype frequencies between T2DM patients and control groups. The frequencies follow the Hardy–Weinberg equilibrium, and the A allele is the major allele and the C allele is the minor allele. The frequency of the C allele calculated in our study (32.2%) is similar to that found in South Indian (35%) but it less than those observed in Caucasian (47%), Chinese (69%), Japanese (62%), and African (81%) populations.<sup>8</sup> The relationship of the rs1121617 variant to glycemic response as investigated in combined meta-analysis of small cohort studies, suggested that the rs1121617 C allele might be considered the first common susceptibility locus associated with successful treatment in patients with T2DM.<sup>17,27</sup> This is consistent with results, which showed T2DM patients carrying the A/A and A/C genotypes of *ATM* rs1121617 variant had significantly higher levels of HbA1c than the carriers of the C/C genotype, thus, the minor allele C is the protective allele for this variant. In contrast to our results, C carriers in the Diabetes Prevention Program showed no significant differences in treatment effects on insulin sensitivity, FBS, and HbA1c compared to A carriers.<sup>25</sup> This could be due to the sample size, period of treatment, or race differences. Replication studies in a relatively large population in a multiethnic diabetic cohort are needed to confirm the role of rs628031 and rs461473 variants of *SLC22A1* and rs1121617 polymorphism of *ATM* on glycemic response to treatment.

## Conclusion

In summary, we found that rs628031 and rs461473 of the *SLC22A1* gene and rs1121617 of *ATM* polymorphisms may interact to affect the risk of T2DM by altering the glycemic parameters and other factors in Saudi populations. Our data indicate that T2DM patients with G/G genotype of both rs628031 and rs461473 *SLC22A1* variants and A/A genotype of rs1121617 polymorphism of the *ATM* gene may influence the glycemic response of T2DM patients. In addition, *SLC22A1* variants rs628031 and rs461473 could be risk factors for obesity and cardiovascular disease in T2DM as these variants were associated with BMI and triglycerides.

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## Disclosure

The authors declare no conflicts of interest in this work.

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