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mTOR gene variant rs2295080 might be a risk factor for atherosclerosis in Iranian women with type 2 diabetes mellitus

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Abstract

Background Type 2 diabetes mellitus, one of the most prevalent metabolic disorders worldwide, is closely linked with an enhanced risk of atherosclerosis. However, the molecular mechanism of this linkage is not still clear. Genetic variations in the *mTOR* gene may increase the susceptibility of individuals to these diseases.

Methods One hundred nine diabetic patients and 375 healthy subjects participated in this study. *mTOR* Single Nucleotide Polymorphism (SNP) rs2295080 was determined using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP).

Results Comparison of genotypic, allelic, and genotypic combination frequencies between cases and controls revealed no significant result. Nevertheless, the frequency of rs2295080 GT + TT genotype was significantly more in diabetic women with atherosclerosis compared with those without atherosclerosis ($p = 0.047$). Besides, the rs2295080 G allele was more frequently detected in diabetic women without atherosclerosis compared to those with atherosclerosis ($p = 0.046$).

Conclusion The rs2295080 GT + TT genotype predisposes Iranian diabetic women to atherosclerosis, while the rs2295080 G allele protects them against atherosclerosis. However, additional experiments using larger sample sizes are needed to verify this result.

Keywords Type 2 diabetes mellitus, *mTOR*, Atherosclerosis, Single nucleotide polymorphism, SNP

Background

Type 2 Diabetes Mellitus (T2DM) is a challenging public health burden and may result in macro- and microvascular complications [1]. Atherosclerosis, as the major macrovascular complication of T2DM, is the leading cause of morbidity and mortality, especially in low- and middle-income countries [2–4]. The exact molecular mechanisms of these chronic diseases are not yet well understood [2, 5, 6]. The PI3K/AKT/mTOR signaling pathway is required for the normal metabolism of the cells. This pathway has been studied in a variety of human diseases such as cancer [7, 8], diabetes [9], atherosclerosis [10], cardiovascular disease [11] and obesity [12]. Mammalian Target of Rapamycin (mTOR) is

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an intracellular molecule that acts as a hub within this pathway [13]. mTOR senses the cellular and environmental cues, such as growth factors, nutrients, and energy then regulates the phosphorylation of intracellular proteins which are crucial for cellular metabolism, survival, homeostasis, growth, and differentiation [14, 15]. Although mTOR pathway critically is implicated in the progression of several metabolic and inflammatory disorders including aging, tumorigenesis, and diabetes, its exact molecular mechanisms are still controversial [2, 6, 16, 17]. Dysfunction of the mTOR might play an important role in the development of T2DM and atherosclerosis [18, 19]. Impairment of mTOR can lead to insulin resistance and obesity which in turn exacerbates and creates a vicious cycle in disease development [20]. Numerous research have used Single Nucleotide Polymorphisms (SNPs) to assess their possible effects on susceptibility to various diseases [21–23]. Indeed, these single-base pair substitutions are the most common type of genetic variation among individuals that may influence the binding of transcription factors, the splicing, conformation, and stability of mRNA, and the expression of genes and thereby may affect disease susceptibility [24]. The 156 kb *mTOR* gene is located on chromosome 1p36.2 and contains 60 exons [25]. Numerous studies have investigated the role of rs2295080, a functional polymorphism in the *mTOR* promoter region, in the development and progression of several diseases [26, 27]. This SNP might affect *mTOR* gene expression, as well as, protein function and stability [28]. In this study the possible association between rs2295080 and susceptibility to T2DM and atherosclerosis was evaluated in an Iranian population.

Methods

Subjects

The study recruited 109 diabetic patients from Fars province, Iran, including 57 males and 52 females with a mean age of 58. 9 ± 24.2 years. Patients were selected from hospitals affiliated with Shiraz University of Medical Sciences. The criteria for the diagnosis of T2DM were: HbA1C ≥ 6.5% according to the National Glycohemoglobin Standardization, fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l), 2-hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test, and in patients with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose of ≥ 200 mg/dl (11.1 mmol/l) [29]. The diagnostic criteria for clinical atherosclerosis were established based on the degree of stenosis observed in the main coronary arteries during diagnostic angiography by a cardiologist. Specifically, stenosis equal to 50 or more in at least one of the main coronary arteries was considered positive while lower than 50 was negative for atherosclerosis [30, 31]. A control group of 375 healthy volunteers from the Fars Blood Transfusion Center with a mean age of 47.32 ± 9.75 years including 213 males and 162 females was recruited for this study. The control group was age and sex-matched with the case group and had neither diabetes nor atherosclerosis confirmed through clinical examinations and self-reported forms.

The study was done in keeping with the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) and was evaluated and approved by the Ethics Committee of Shiraz University of Medical Sciences Shiraz, Iran (the code of ethical approval was IR.SUMS.REC.1401.382). All participants provided informed consent for blood donation and data publication. Detailed information about the patients, including their age, body mass index (BMI), hypertension status, and smoking status was collected (Table 1).

DNA extraction and genotyping analysis

A total of 4 ml of whole blood sample was collected from each participant into EDTA tubes. Genomic DNA was extracted using the salting out method, and all DNA samples were stored at -20 °C until testing. The *mTOR* rs2295080 was genotyped using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). Table 2 shows details of the used primers and the required restriction enzyme. The amplification process involved an initial denaturation at 95 °C for 5 min, followed by 30 cycles of denaturation at 95 °C for 30 s, annealing at 56 °C for 30 s, and extension at 72 °C

Table 1 Demographic and clinical findings of participants

Variables			Patients (*N*%)	Healthy controls (*N*%)
Number			109	375
Age (years)			58. 9 ± 24.2	47.32 ± 9.75
Gender		Male	57 (52.3)	213 (56.8)
		Female	52 (47.7)	162 (43.2)
Body Mass Index	< 25	Male	18 (54.5)	-
		Female	15 (45.5)	34 (100)
	> 25	Male	29 (49.2)	-
		Female	30 (50.8)	21 (41.2)
Hypertension	Yes	Male	29 (43.9)	-
		Female	37 (56.1)	-
	No	Male	17 (70.8)	-
		Female	7 (29.2)	-
Smoking history	Yes	Male	11 (78.6)	-
		Female	3 (21.4)	-
	No	Male	37 (46.8)	-
		Female	42 (53.2)	-

Table 2 The primer sequence, restriction enzymes, and fragment length of the *mTOR*gene SNP r**s**2295080

Primer Sequence (5′ to 3′)	Product size (bp)	Restriction enzyme	Fragment Length (bp)
F: GACATTACGCCGCCCTAGAG R: TGGTTTGTCTATTTGAACAGTCC	297	BseGI	GG:297 GT: 297, 170, 127 TT: 170,127

for 30 s, with a final extension step at 72 °C for 5 min. The PCR products were then digested with the BseGI restriction enzyme. Finally, the PCR products were analyzed using a 2.5% agarose gel stained with DNA safe stain and visualized under ultraviolet light (Fig. 1).

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software (version 26) and EPI INFO 7.2.2.6 software were used to conduct statistical analyses. The OSSE online tool available at http://osse.bii.a-star.edu.sg/calculation1.php was used to estimate the sample size. Deviation from Hardy-Weinberg equilibrium was analyzed using the website https://wpcalc.com/en/equilibrium-hardy-weinberg. To remove the confounding effects of variables, binary logistic regression analysis was performed. All tests were two-sided with a significant level of *P*-value < 0.05.

Results

Genotype and allele frequencies of rs2295080 in diabetic patients and healthy controls

The studied SNP followed the Hardy-Weinberg Equilibrium (patient group: $p=0.090$, control group: $p=0.068$). As shown in Table 3, the most frequent genotype and allele in diabetic patients and healthy controls were TT and T, respectively. However, comparing genotypes and allele frequency between cases and controls did not show a statistically significant difference.

Comparison of rs2295080 between diabetic patients with and without atherosclerosis

According to the angiographic data, diabetic patients were divided into those with atherosclerosis and those without. As shown in Table 4, comparing genotypes and alleles of rs2295080 revealed a significantly higher frequency of the GT + TT genotype among diabetic women with atherosclerosis compared to those without atherosclerosis ($p=0.047$). Moreover, G allele frequency was significantly more in diabetic women without atherosclerosis ($p=0.046$).

The association between rs2295080 and clinical characteristics of diabetes

Evaluation of the genotypes and alleles of rs2295080 with body mass index (BMI), smoking, and blood pressure status of diabetic patients revealed no significant differences (data not shown).

Discussion

In this study, the possible association between *mTOR* gene polymorphism rs2295080 and susceptibility to type 2 diabetes and its major complication, atherosclerosis was evaluated. The PI3K/AKT/mTOR signaling pathway

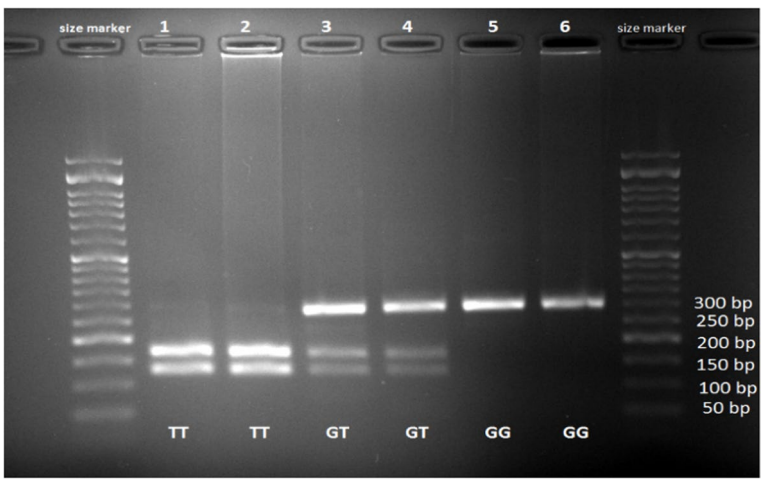

Fig. 1 PCR-RFLP image of the *mTOR* gene polymorphism rs2295080 shows TT (lanes 1 and 2), GT (lanes 3 and 4), and GG (lanes 5 and 6) genotypes

Table 3 Genotype and allele frequencies of rs2295080 polymorphism in type 2 diabetic patients and healthy controls

SNP		Patients ($n = 109$) N (%)			Controls ($n = 375$) N (%)			OR (95%CI)			p-value		
		Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
rs2295080													
Genotypes	TT	52 (47.7)	28 (49.5)	24 (46.0)	184 (49.0)	106 (50.0)	78 (48.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	GT	42 (38.3)	22 (38.5)	20 (38.5)	139 (37.0)	87 (41.0)	52 (32.0)	1.1 0.3–3.1	1.04 0.2–4.1	1.36 0.2–7.3	0.85	0.95	0.71
	GG	15 (14.0)	7 (12.0)	8 (15.5)	52 (14.0)	20 (9.0)	32 (20.0)	0.01 0.02–0.4	0.01 0.04–0.2	0.01 0.02–0.45	0.99	0.99	0.99
Alleles	T	145 (66.5)	78 (68.0)	67 (64.5)	507 (67.0)	299 (70.0)	208 (64.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	G	73 (33.5)	36 (32.0)	37 (35.5)	243 (33.0)	127 (30.0)	116 (36.0)	1.79 0.75–4.2	1.3 0.42–4.2	1.7 0.4–6.8	0.18	0.63	0.44
Genotype combination	TT	52 (47.7)	28 (49.0)	24 (46.0)	184 (49.0)	106 (49.7)	78 48.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	GT + GG	57 (52.3)	29 (51.0)	28 (54.0)	191 (51.0)	107 (50.3)	84 (52.0)	1.3 0.4–3.7	1.1 0.2–4.4	1.1 0.19–6.1	0.6	0.8	0.9
	GG	15 (14.0)	7 (12.0)	8 (15.0)	52 (14.0)	20 (9.0)	32 (19.7)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	GT + TT	94 (86.0)	50 (88.0)	44 (85.0)	323 (86.0)	193 (91.0)	130 (80.3)	1.7 0.01–0.2	9.7 0.01–0.1	1.7 0.6–1.09	0.99	0.99	0.99

Table 4 The association between rs2295080 and atherosclerotic complication of type 2 diabetes

SNP		Atherosclerosis (Yes) *N* (%)			Atherosclerosis (No) *N* (%)			OR (95%CI)			*p*-value		
		Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
rs2295080													
Genotypes	TT	27 (53)	16 (52.0)	11 (55.0)	25 (43.0)	12 (46.0)	13 (41.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	GT	17 (33.3)	9 (29.0)	8 (40.0)	25 (43.0)	13 (50.0)	12 (37.0)	0.64 0.26–1.6	0.46 0.12–1.6	0.9 0.24–3.8	0.34	0.58	0.97
	GG	7 (13.7)	6 (19.0)	1 (5.0)	8 (14.0)	1 (4.0)	7 (22.0)	0.38 0.11–1.3	1.9 0.17–21.6	5.9 0.6–55.8	0.14	0.24	0.054
Alleles	T	71 (69.0)	41 (66.0)	30 (75.0)	75 (65.0)	37 (71.0)	38 (59.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	G	31 (31.0)	21 (34.0)	10 (25.0)	41 (35.0)	15 (29.0)	26 (41.0)	1.6 0.9–3.1	1.08 0.4–2.7	2.6 1.01–6.7	0.1	0.86	**0.046**
Genotype combination	TT	27 (52.9)	16 (51.6)	11 (55.0)	25 (43.1)	12 (46.2)	13 (40.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	GT + GG	24 (47.1)	15 (48.4)	9 (45.0)	33 (56.9)	14 (53.8)	19 (59.4)	1.7 0.76–4.1	1.6 0.4–5.5	1.8 0.5–6.5	0.17	0.43	0.31
	GG	7 (13.7)	6 (19.4)	1 (5.0)	8 (13.8)	1 (3.8)	7 (21.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)			
	GT + TT	44 (86.3)	25 (80.6)	19 (95.0)	50 (86.2)	25 (96.2)	25 (78.1)	2.1 0.6–6.9	0.3 0.03–3.6	9.8 1.03–92.8	0.21	0.3	**0.047**

plays a vital role in glucose homeostasis and regulates the response of cells to extracellular stimuli such as insulin [32]. In this manner, it regulates the translocation of glucose transporter type 4 to the cell surface, the uptake of glucose, the synthesis of glycogen, the suppression of glucose production, triglyceride synthesis, and insulin-induced mitogenesis [33]. If any of these functions are impaired, hyperglycemia and diabetes can occur [34]. On the other hand, T2DM can trigger the development of atherosclerosis or further accelerate its progression [1]. Elevated blood glucose levels, dyslipidemia, and other metabolic changes associated with disease development are involved in the pathogenesis of atherosclerosis at almost every stage of the atherogenic process [5]. More evidence has indicated that the mTOR signaling pathway is activated by atherosclerotic ox-LDL via PI3K/Akt which is required for vascular smooth muscle cell proliferation [35]. Genetic variations in this signaling pathway might influence the development of T2DM and atherosclerosis. These variants may alter the expression of *mTOR*, thereby deregulating the signaling pathway involved in disease initiation. A recent study by Hu Li et al. evaluated the possible association between some polymorphisms in the *mTOR* gene, including rs2295080 (G > T), rs2536 (T > C), rs1034528 (G > C), and rs11121704 (C > T) with atherosclerosis and the risk of coronary heart disease (CHD) and its prognosis among a Chinese population [36]. They proved that rs2295080 TT genotype and T allele; rs2536 CC + CT and CC genotypes, and C allele; rs1034528 CC + GC genotypes, and C allele are associated with significantly increased risk of CHD onset. Furthermore, they demonstrated that rs2295080 TT, TT + GT genotypes, and T allele were associated with poor atherosclerosis and CHD prognosis. Similar results were seen for the rs2536 CC + CT genotype and the C allele. However, they found no significant association between rs11121704 and atherosclerosis and the risk of CHD. Few studies have investigated the effect of *mTOR* polymorphisms on the risk of T2DM. A study reported that the intron variant rs4845856 is not associated with the development of T2DM [33]. As far as we know, our study is the first to evaluate the possible role of *mTOR* rs2295080 in the pathogenesis of atherosclerosis among diabetic patients. In line with the study by Hu Li et al. mentioned above, our results revealed a significantly higher frequency of the rs2295080 GT + TT genotype in diabetic women with atherosclerosis compared with those without atherosclerosis. Interestingly, a higher frequency of the rs2295080 G allele was also indicated among diabetic women without atherosclerosis. These findings indicate the GT + TT genotype increases the susceptibility of Iranian diabetic women to atherosclerosis while the G allele is a protective factor against it. In support, another study has shown that the rs2295080 G allele decreases the susceptibility of Han Chinese females to Microscopic Polyangiitis (MPA) [37]. Several other studies have demonstrated the importance of this polymorphism in different disease states.

The significance of rs2295080 has been shown in various malignancies, such as urinary tract cancer [38, 39], colorectal adenocarcinoma [40], leukemia [41], gastric cancer [42], breast cancer [43], prostate and liver malignancies. These studies have found that the TT genotype and the T allele increase the risk of cancer, while the GG genotype and the G allele are protective. Functional assays for the *mTOR* gene have revealed that the rs2295080 G allele significantly decreases its transcriptional activity [38] while the T allele increases its expression and at the same time, affects the binding of other transcription factors that dysregulate its expression [40, 42]. On the contrary, a study in Finland showed that the TT genotype and the T allele of rs2295080 reduce the risk of age-related macular degeneration (AMD) [44]. In addition, a German study on liver transplant recipients suggested that the rs2295080 GG genotype is associated with the development of new-onset diabetes mellitus following Everolimus treatment [45]. Such discrepancy might be due to the different ethnicity, the synergic/suppressing effects of other genes inside the mTOR signaling pathway, epigenetics, and exposure to different environmental factors. Understanding the relationship between gene variants and susceptibility to diseases and their complications can pave the way for a better understanding of the mechanism of disease initiation and progression, and might contribute in the development of new therapeutic modalities. Targeting mTOR is now an effective therapeutic approach in many diseases, including Alzheimer's, RA, and cancer therapy [46–49]. *mTOR* polymorphisms might resist some therapeutic procedures and be a possible explanation for why some mTOR inhibitory drugs are not beneficial [45, 50]. For instance, new-onset diabetes mellitus was reported following the mTOR inhibitor Everolimus administration in some liver transplant recipients who had rs2295080 CC genotype [45]. So, the existence of *mTOR* variants requires further analyses and consideration when making treatment choices. It seems desirable to design studies investigating the effect of genetic variation on the quality of resistance to mTOR inhibitors. Accordingly, Prospective randomized clinical trials that include *mTOR* genotype testing would be promising. Our study had some limitations such as the limited sample size, not considering other functional *mTOR* SNPs, and thereby not evaluating the effect of linkage between adjacent SNPs, and not confirming PCR-RFLP results with sequencing.

Conclusion

Our study suggested that the GT + TT genotype increases the susceptibility of Iranian diabetic females to atherosclerosis while the G allele could be a protective factor against it. However, more research with a larger sample size is needed to confirm these results. Moreover, functional and linkage analyses would elucidate the precise role of rs2295080 in the pathogenesis of T2DM and atherosclerosis.

Abbreviations

T2DM	Type 2 Diabetes Mellitus
mTOR	mammalian Target of Rapamycin
SNP	Single Nucleotide Polymorphism
BMI	body mass index
PCR-RFLP	Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
SPSS	Statistical Package for Social Sciences
ORs	Odds ratios
CIs	Confidence intervals
MPA	Microscopic Polyangiitis
AMD	Age-related Macular Degeneration

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

AZ performed the experiments and analysis and prepared a preliminary manuscript draft. SK helped in designing the study. GD and MD conceived and designed the study, wrote the paper, and critically revised the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Data Availability

Data is provided within the manuscript or supplementary information files

Declarations

Ethics approval and consent to participate

Our study was approved by the Ethics Committee of the Shiraz University of Medical Science (SUMS) and was conducted following the ethical principles outlined in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Before participation, all the individuals provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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