

# Vitamin D receptor gene polymorphisms in type 1 diabetes mellitus: a new pattern from Khorasan province, Islamic Republic of Iran

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تعدد أشكال جين مستقبلات الفيتامين "د" في النمط الأول من السكري: نموذج جديد من منطقة خراسان في جمهورية إيران الإسلامية  
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الخلاصة: تختلف الترابطات المسجلة بين تعدد أشكال مستقبلات الفيتامين "د" (VDR) والنمط الأول من السكري في ما بين المجموعات العرقية. وقد درس الباحثون العلاقة بين النمط الأول من السكري وبين أربعة أشكال متعددة لجين مستقبلات الفيتامين "د" (وهي: *Bb*, *Ff*, *Aa*, *Tt*) لدى الإيرانيين. وضمت الدراسة مجموعة مكونة من 69 مريضاً بالنمط الأول من السكري، و 45 شخصاً غير مريض بالسكري. وجرى تحليل معدل انتشار تعدد أشكال مستقبلات الفيتامين "د" في 4 مواقع لاقطاع الشد في ذلك تحليل *BsmI*, *FokI*, *ApaI*, *TaqI* في مجموعتي المرضى والشواهد. وكان تكرار ثلاثة أنماط جينية هي (*Aa*, *Ff*, *Bb*) أعلى بدرجة يُعتدُّ بها إحصائياً في مجموعة المرضى. ولم تُشاهد علاقة يُعتدُّ بها إحصائياً بين تعدد أشكال جين مستقبل الفيتامين "د" وبين نماذج بدء السكري. كما لم تُشاهد فوارق يُعتدُّ بها إحصائياً بين تكرار النمط الجيني وبين المضاعفات المزمنة للسكري، في حين شوهدت علاقة يُعتدُّ بها إحصائياً بين النمط الجيني *Ff* وبين الحمض الكيتوني. وقد تبين أن نتائج هؤلاء الباحثين تختلف عن الدراسات السابقة لتعدد الأشكال في مناطق أخرى.

ABSTRACT Reported associations between vitamin D receptor (VDR) polymorphism and type 1 diabetes mellitus vary across ethnic groups. We studied the association between type 1 diabetes and 4 VDR gene polymorphisms (*Bb*, *Ff*, *Aa* and *Tt*) in an Iranian population. A group of 69 patients with type 1 diabetes mellitus and 45 unrelated healthy subjects were recruited. The prevalence of VDR polymorphisms in 4 restriction fragment length polymorphism sites including *BsmI*, *FokI*, *ApaI* and *TaqI* were analysed in patients and controls. The frequencies of 3 genotypes (*Aa*, *Ff* and *Bb*) were significantly higher in the patient group. The relationship between VDR gene polymorphisms and onset pattern of diabetes was not significant. There were no significant difference between the genotype frequencies and chronic complications of diabetes, but the relationship between the *Ff* genotype and ketoacidosis was significant. Our results differ from previous polymorphism studies in other regions.

## Polymorphismes du gène du récepteur de la vitamine D et diabète de type 1 : un nouveau modèle dans la province de Khorasan (République islamique d'Iran)

RÉSUMÉ Les associations observées entre le polymorphisme du récepteur de la vitamine D et le diabète de type 1 varie en fonction des groupes ethniques. Nous avons étudié l'association entre le diabète de type 1 et quatre polymorphismes du gène du récepteur de la vitamine D (génotypes *Bb*, *Ff*, *Aa* et *Tt*) dans une population iranienne. Un groupe de 69 patients atteints de diabète de type 1 et 45 témoins en bonne santé sans lien entre eux ont été recrutés pour cette étude. La prévalence des polymorphismes de ce gène sur quatre sites de polymorphisme de la longueur des fragments de restriction (notamment *BsmI*, *FokI*, *ApaI* et *TaqI*) a été analysée dans les deux groupes. La fréquence de trois génotypes (*Aa*, *Ff* et *Bb*) était nettement supérieure dans le groupe des patients. Le lien entre les polymorphismes géniques du récepteur de la vitamine D et l'apparition d'un diabète n'était pas significatif. Aucune différence importante n'a été observée entre la fréquence des génotypes et les complications chroniques du diabète. Toutefois, le lien entre le génotype *Ff* et l'acidocétose était fort. Nos résultats diffèrent des études antérieures sur le polymorphisme dans d'autres régions.

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## Introduction

Type 1 diabetes mellitus (DM) is a common autoimmune endocrinopathy that results from an interaction of environmental and genetic factors. This interaction is believed to lead to immune destruction of insulin-producing beta cells by T-cell infiltration of the pancreatic islets [1]. In addition to its calciotropic effect, vitamin D has potent non-calcaemic effects and is involved in the modulation and regulation of immune systems [2–6]. Vitamin D deficiency has been shown to accelerate the onset of type 1 DM [7]. Moreover, vitamin D deficiency leads to impaired insulin secretion, which is reversible by 1,25-dihydroxyvitamin D administration [8]. Other studies suggest that the active metabolite of vitamin D decreases the incidence and development of autoimmune diseases such as type 1 DM and also acts as an immunosuppressant agent [9,10]. The biological effect of vitamin D is thought to occur by binding to the vitamin D receptor (VDR) which belongs to the steroid receptor superfamily and is widely expressed in many cell types including lymphocytes (activated T lymphocytes, B cells), antigen-presenting cells (including monocytes, macrophages, dendritic cells) and pancreatic islet cells [11–13].

Although many polymorphisms exist in the VDR gene, their effect on VDR protein function and signalling is unknown [14]. Based on the effect of the VDR ligand on immune function, an association between type 1 DM and VDR polymorphisms is likely. The effect of VDR polymorphisms on insulin secretion has been reported before [15]. Four major polymorphic sites have been described within the VDR gene. A polymorphic *FokI* site in exon-2 results in an alternative transcription initiation site, leading to a protein variant with 3 additional amino acids at the amino terminus [4]. Polymorphic *BsmI* and *ApaI* sites are present in intron-8, and a

silent T to C substitution creates a *TaqI* polymorphic site in exon-9 [16].

An association between VDR polymorphism and type 1 DM has been reported in some studies; however, it appears to vary across ethnic groups [17–23]. The aim of this study was to investigate the relationship of VDR gene polymorphism to the risk of type 1 DM and its association with the onset pattern of diabetes (acute or slow onset) in an Iranian population in Khorasan province.

## Methods

### Sample collection

The study was carried out in Mashhad, Islamic Republic of Iran, during 2006–07. Patients were drawn from the Parsian diabetes clinic, which is a referral centre for diabetic patients and cares for more than 500 patients with type 1 DM. Blood samples were obtained from 69 Iranian type 1 DM patients (41 females/28 males) diagnosed with type 1 DM according to World Health Organization criteria (pancreatic beta-cell destruction as the primary cause of diabetes, and tendency to ketoacidosis), under age 35 years and C-peptide-negative. Another group of 45 unrelated healthy volunteers (26 females/19 males) with a socioeconomic status similar to that of the patients, were also recruited from classmates or friends of the patients.

Demographic and basic clinical variables were collected such as age, sex, time of onset of diabetes, time of starting insulin treatment and history of ketoacidosis and complications such as hypertension, retinopathy, nephropathy, dyslipidaemia, concomitant autoimmune disorders. The patients were divided into 2 groups: acute onset (< 6 months from onset of diabetes to start of insulin treatment); and slow onset (> 12 months from diabetes onset to insulin treatment).

All patients gave informed voluntary consent to participate in the study according to the protocol approved by the local ethics committee of Mashhad University of Medical Sciences and in accordance with the ethical standards of the Helsinki Declaration.

### DNA isolation and PCR experiments

Blood samples were collected in EDTA tubes and genomic DNA was extracted using the salting out method. The *BsmI*, *FokI*, *ApaI* and *TaqI* polymorphic sites were considered. Polymerase chain reaction (PCR) amplification was performed using 3 sets of primers—VDR1 (for *BsmI*), VDR2 (for *FokI*), and VDR3 (for both *ApaI* and *TaqI*)—as described previously [17,22], using the Techgene thermocycler (Techne). After initial denaturation for 5 min. at 95 °C, samples were subjected to 30 cycles of amplification, 25 s at 94 °C, 20 s at the relevant primer pair annealing temperature (Table 1) and 20 s at 72 °C. The final step was a 5 min. hold at 72 °C. Amplified DNA was digested overnight with suitable amounts of reference restriction enzymes (Fermentas) in the restriction protocol at 37 °C or 4 h at 55 °C according to the manufacturer's instructions (Table 1). Digestion products were electrophoresed on 3% agarose gel containing 0.4 mg/L ethidium bromide. The polymorphism was documented by photographing under UV illumination.

### Polymorphism analysis

All data concerning the 4 restriction enzymes and their restriction patterns are summarized in Table 1. Aliquots of 0.1 U of *BsmI*, *FokI* and *ApaI* and 3U of *TaqI* restriction enzymes (Fermentas, Lithuania) and 2 µL buffer were added to 4 µL of the VDR PCR products. The alleles were designated as *B* (650 bp and 175 bp fragments) and *b* (825 bp fragment) for *BsmI*, *F* (196 bp and 69 bp fragments) and *f* (265 bp) for *FokI*

Table 1 Characteristic features of the 4 studied polymorphisms in the vitamin D receptor (VDR) gene

Polymorphism	Location in VDR gene	Restriction site	Digested alleles	Primer sequence	Annealing temperature (°C)	Digestion protocol	Amplicon length (bp)	Restricted fragments (bp)
<i>BsmI</i>	Intron-8	G <sup>+</sup> AATGCC(1/-)↓	B, b	Forward: 5'-CAA CCA AGA CTA CAA GTA CCG CGT CAG TGA-3' Reverse: 5'-AAC CAG CCG GAA GAG GTC AAG GG-3'	63	37 °C overnight	825	650, 175
<i>FokI</i>	Exon-2	GGATG(9/13)↓	<i>F, f</i>	Forward: 5'-AGC TGG CCC TGG CAC TGA CTC TGC TCT-3' Reverse: 5'-ATG GAA ACA CCT TGC TTC TTCTCC CTC-3'	68	37 °C overnight	265	196, 69
<i>ApaI</i>	Intron-8	GGGCC↓C	<i>A, a</i>	Forward: 5'-CAG AGCATG GAC AGG GAG CAA-3' Reverse: 5'-GCA ACT CCT CAT GGC TGA GGT CTC-3'	62	37 °C overnight	740	530, 210
<i>TaqI</i>	Exon-9	T↓CGA	<i>T, t</i>	Forward: 5'-CAG AGC ATG GAC AGG GAG CAA-3' Reverse: 5'-GCA ACT CCT CAT GGC TGA GGT CTC-3'	62	55 °C 4 h	740	PS+: 290, 245, 205 PS-: 495, 245

PS+ = restriction pattern when the polymorphic site is present; PS- = restriction pattern without polymorphic site.

and *A* (530 bp and 210 bp) and *a* (740 bp) for *ApaI*. *TaqI* has 2 binding sites on the PCR product, one product a 495 bp and a 245 bp fragment (*t*) and the other at the single nucleotide polymorphism site in the presence of which the 495 bp fragment will be cut into a smaller 290 bp piece and a 205 bp piece (*T*).

### Statistical analysis

Data were analysed using *SPSS*, version 11.5 statistical software. Comparisons of genotype frequencies between groups were performed using the t-test. The chi-squared test was used for analysis of the difference between the 2 groups. *P*-value < 0.05 was considered significant.

### Results

The patients were 28 males (40.6%) and 41 females (59.4%). The mean age of patients was 22.2 (SD 8.7) years and the mean age onset of diabetes was 13.4 (SD 6.1) years. Family history of DM was positive for 26 patients (37.7%). The frequency of complications of diabetes, including history of ketoacidosis, hypertension, retinopathy, nephropathy and dyslipidaemia, are shown in Table 2. There were 50 patients (72.5%) with acute onset of diabetes and 19 patients (27.5%) with chronic onset. The control group consisted of 19 (42.2%) men and 26 (57.8%) women with a mean age of 19.7 (SD 6.2) years.

The distributions of VDR gene polymorphism in patients and control groups are shown in Table 3. The genotype frequencies were higher in the patients than the controls for the *bb* genotype (42.6% versus 40.0%, *P* = 0.14) and the *TT* genotype (49.3% versus 44.4%, *P* = 0.057) although the differences were not significant. However, the frequencies of genotypes were significantly higher in the patient group versus controls for the *Aa* genotype (75.4% versus 40.0%, *P* = 0.003), *FF* genotype (55.1% versus 40.0%, *P* = 0.008) and *Bb* genotype (37.7% versus 24.4%, *P* = 0.014).

We stratified type 1 DM patients based on their onset pattern of disease and assessed the relationship to the types of VDR gene polymorphisms (Table 4). The relationship between VDR gene polymorphisms and onset pattern of diabetes was not significant in any of restriction sites. The age of onset of disease did not affect the distribution of genotype frequencies in type 1 DM patients. Moreover, there was no significant difference between the distribution of genotype frequencies (*BsmI*, *ApaI*, *FokI* and *TaqI*) and chronic complications of diabetes, but the relation between the *Ff* genotype and history of ketoacidosis was significant (*P* = 0.04).

The electrophoresis pattern of the 4 restriction enzymes is illustrated in Figure 1.

### Discussion

The molecular mechanisms of pathogenesis of type 1 DM remain to be elucidated. Several studies have recently reported an association

**Table 2** Frequencies of complications in patients with type 1 diabetes mellitus (n = 69)

Complication	Positive		Negative	
	No.	%	No.	%
History of ketoacidosis	39	56.5	30	43.5
Hypertension	2	2.9	67	97.1
Retinopathy	8	11.6	61	88.4
Nephropathy	6	8.7	63	91.3
Dyslipidaemia	14	20.3	55	79.7
Concomitant autoimmune disorders	6	8.7	63	91.3

between type 1 DM and VDR gene polymorphisms. This study demonstrated a significantly higher frequency of *Aa*, *FF* and *Bb* genotypes in the VDR receptor in type 1 DM patients in an Iranian population. The frequency of *bb* and *TT* genotypes were also higher in patients compared with the control group, but the differences were not statistically significant.

Several populations with different genetic background have been studied for the association of type 1 DM and VDR gene polymorphisms, and contradictory results have been shown. The results of the first published study in

southern India showed that the *b* allele of *BsmI* in VDR was more prevalent in type 1 DM patients than healthy controls [18]. Chinese investigators showed in their Han population that the frequency of the *B* allele of *BsmI* site gene was significantly higher in type 1 DM [19]. In a Taiwanese population type 1 DM was also associated with the *B* allele [20]. In Barcelona, Spain, the frequencies of *bb*, and especially combined *bb/FF* genotypes, were higher in type 1 DM patients than in controls [21]. However, in a Finnish population VDR polymorphisms had no association with type 1 DM [24],

**Table 3** Distribution of vitamin D receptor (VDR) gene polymorphisms in patients with type 1 diabetes mellitus and non-diabetic controls

VDR polymorphism	Cases (n = 69)		Controls (n = 45)		P-value
	No.	%	No.	%	
<b><i>BsmI</i></b>					
bb	29	42.0	18	40.0	0.109
BB	14	20.3	16	35.6	0.715
Bb	26	37.7	11	24.4	0.014
<b><i>FokI</i></b>					
ff	6	8.7	7	15.6	0.782
FF	38	55.1	18	40.0	0.008
Ff	25	36.2	20	44.4	0.456
<b><i>Apal</i></b>					
aa	4	5.8	1	2.2	0.180
AA	13	18.8	18	40.0	0.369
Aa	52	75.4	26	40.0	0.003
<b><i>TaqI</i></b>					
tt	7	10.1	8	17.8	0.796
TT	34	49.3	20	44.4	0.057
Tt	28	40.6	17	37.8	0.101

and a study in Santiago on children with type 1 DM demonstrated that the frequency of the *b* allele and *bb* genotype was significantly lower compared with the control group [22]. Surprisingly, a meta-analysis in 2006 also showed that there was no association between VDR gene polymorphisms and type 1 DM risk in case-control and family transmission studies [25].

In our study no significant relationship was found between VDR polymorphisms and the onset pattern of diabetes (acute or chronic). Motohashi et al. in a study of 203 type 1 DM patients compared with healthy controls found that there was a significant difference in the frequency of the *B* allele in the *BsmI* site between acute-onset diabetes and control groups. However, the difference between the slow-onset type 1 DM group and controls was not significant and they concluded that assessment of this VDR gene polymorphism may contribute to prediction of the onset pattern in individuals with a high-risk component of type 1 DM [23].

No significant association was found between VDR gene polymorphisms and chronic complications of diabetes (including nephropathy, retinopathy, dyslipidaemia and hypertension). Taverna et al. in Paris observed 200 patients with type 1 DM and found that the *Tt* genotype was associated with severe retinopathy. In that study, patients with *TT* genotype were low risk for severe diabetic retinopathy [26]. We found no association between VDR gene polymorphisms and diabetic retinopathy. It seems that vitamin D functions may play a role in the pathogenesis of hypertension as a negative endocrine regulator of renin biosynthesis [27] and have a favourable effect on cardiovascular disease [28,29]. Other researchers have also reported an association between the *bb* genotype and severe coronary stenosis [30].

We found a significant relationship between the *Ff* genotype and a history of ketoacidosis among our patients. To

**Table 4** Distribution of vitamin D receptor (VDR) gene polymorphisms in patients with type 1 diabetes mellitus according to history of ketoacidosis and onset of diabetes

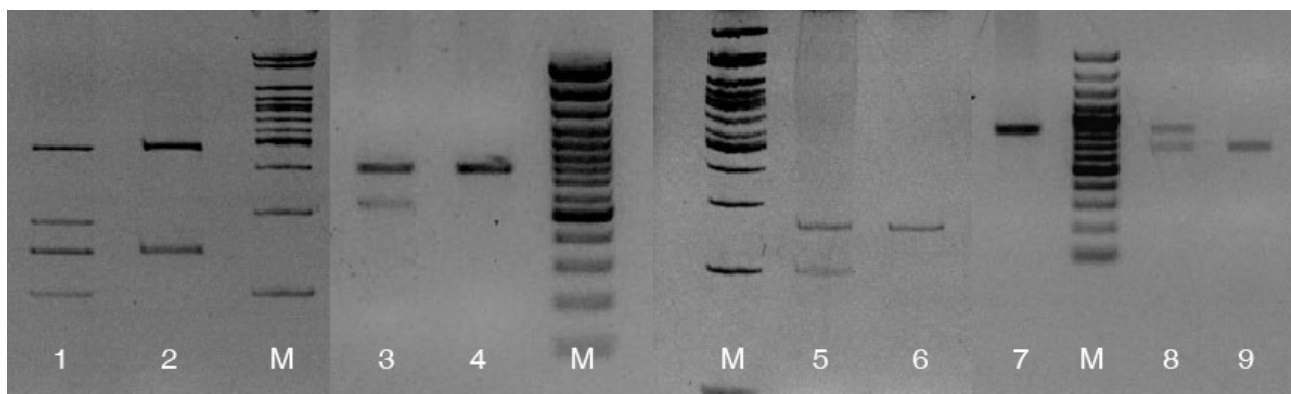
VDR polymorphism	With history of ketoacidosis (n = 39)		Without history of ketoacidosis (n = 30)		P-value	Acute onset (n = 50)		Chronic onset (n = 19)		P-value
	No.	%	No.	%		No.	%	No.	%	
<b>BsmI</b>										
bb	17	43.6	12	40.0	0.36	31	64.0	10	52.6	0.44
BB	6	15.4	8	26.7		5	10.0	5	26.3	
Bb	16	41.0	10	33.3		14	26.0	4	21.1	
<b>FokI</b>										
ff	2	5.1	5	16.7	0.04	2	4.0	2	10.6	0.48
FF	20	51.3	18	60.0		32	64.0	14	73.6	
Ff	17	43.6	7	23.3		16	32.0	3	15.8	
<b>Apal</b>										
aa	2	5.1	2	6.7	0.86	2	4.0	0	0.0	0.21
AA	6	15.4	6	20.0		4	8.0	5	26.3	
Aa	31	79.5	22	73.3		44	88.0	14	73.7	
<b>TaqI</b>										
tt	2	5.1	4	13.3	0.50	0	0.0	1	5.3	0.27
TT	20	51.3	12	40.0		35	70.0	13	68.4	
Tt	17	43.6	14	46.7		15	30.0	5	26.3	

our knowledge this is first report of this association. In a study performed on 134 unrelated patients, investigators found that the *ff* genotype frequency was significantly higher in type 1 DM patients than controls, although the relationship between type 1 DM and chronic complications of diabetes was not analysed [31]. In a Chinese population, the *F* allele of the *FF* genotype

showed a higher prevalence in patients compared with controls. The *FF* genotype was suggested as a marker for type 1 DM in this population. However, the authors did not analyse the relation of this genotype with type 1 DM associated complications.

This is the first report comparing the frequencies of all 4 known sites of the VDR gene in healthy and type

1 DM Iranian population. It seems that environmental factors that influence levels of active vitamin D in humans are complex and a significant difference exists between vitamin D functions and VDR polymorphisms. It further confirms that the association between VDR polymorphisms and type 1 DM varies across different ethnic groups.



**Figure 1** Digestion results of the 4 polymorphism sites. *TaqI* digestion: *Tt* (lane 1), *tt* (lane 2); *Apal* digestion: *Aa* (lane 3), *aa* (lane 4); *FokI* digestion: *Ff* (lane 5), *ff* (lane 6); *BsmI* digestion: *bb* (lane 7), *Bb* (lane 8), *BB* (lane 9). M: 100 bp DNA ladder (Fermentas)

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