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Vitamin D receptor gene polymorphisms and haplotypes (*Apa* I, *Bsm* I, *Fok* I, *Taq* I) in Turkish psoriasis patients

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Psoriasis is an inflammatory disease characterized by increased squamous cell proliferation and impaired differentiation. Vitamin D, Calcitriol, and its analogues are successfully used for psoriasis therapy. However, it is unknown why some psoriasis patients are resistant to Vitamin D therapy. Vitamin D mediates its activity by a nuclear receptor. It is suggested that polymorphisms and haplotypes in the VDR gene may explain the differences in response to vitamin D therapy.

Material/Methods: In this study, 102 psoriasis patients and 102 healthy controls were studied for VDR gene polymorphisms. The *Fok* I, *Bsm* I, *Apa* I and *Taq* I polymorphisms were examined by PCR-RFLP, and 50 subjects received vitamin D therapy to evaluate the association between VDR gene polymorphisms and response to vitamin D therapy. Existence of cutting site is shown by capital letters, and lack was shown by lower case. The haplotypes were analysed by CHAPLIN.

Results: There was significant difference in allele frequency of T and genotype frequency of Tt between cases and controls (p values 0.038 and 0.04, respectively). The Aa and bb genotypes were significantly higher in early onset than late onset psoriasis (p values 0.008 and 0.04, respectively). The genotypes Ff, ff and TT are significantly different between vitamin D3 therapy responders and non-responders (p values 0.04, 0.0001, 0.009, respectively). To the best of our knowledge, this is the first report showing importance of VDR gene haplotypes in psoriasis, the significance of the Wald and LR (Likelihood Ratio) statistics (p=0,0042) suggest that FfBbAatt is a disease-susceptibility haplotype.

Conclusions: Haplotype analysis is a recent and commonly used method in genetic association studies. Our results reveal a previously unidentified susceptibility haplotype and indicate that certain haplotypes are important in the resistance to vitamin D3 therapy and the onset of psoriasis. The haplotypes can give valuable data where genotypes unable to do.

key words: haplotype • polymorphism • psoriasis • vitamin D • VDR • Turkish

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Background

Psoriasis is a genetic disorder of the skin causing inflammatory disease, characterized by increased squamous cell proliferation and impaired differentiation. The CARD14 gene was recently identified as the first gene directly linked to Psoriasis [1]. It is reported that more than 15 mutations and some polymorphisms are associated with the disease [2]. $1,25(OH)_2D_3$ is the endogenously produced, hormonally active form of vitamin D_3. In addition to the known effect of $1,25(OH)_2D_3$ on controlling calcium and bone metabolism, it inhibits proliferation and induces terminal differentiation of cultured human keratinocytes. It can also modulate the immune system in a variety of ways, enhancing immunosuppressive and anti-inflammatory pathways, which are its possible mechanisms of action in psoriasis lesions. Serum Vit D_3 levels can be low in psoriasis patients due to some extrinsic factors such as dietary or geographically low sun exposure. However, decreased levels of Vit D_3 are not caused by vitamin D deficiency [3–6]. $1,25(OH)_2D_3$ elicits its action on target tissues through the vitamin D receptor (VDR). The receptor-hormone complex binds to hormone response elements in regulatory regions of target genes, and modulates the gene transcription. However, it has been noted that cultured fibroblasts and keratinocytes from some psoriatic patients have partial resistance to $1,25(OH)_2D_3$-mediated anti-proliferative activity [6,7]. Although therapeutic efficacy of 1α,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] and its analogues have been tested and proved to be effective for the treatment of psoriasis [8], clinical response to $1,25(OH)_2D_3$ treatment is variable in patients [9]. Experiments examining the anti-proliferative effects of calcitriol demonstrated that about 25% of psoriatic patients possessed dermal fibroblasts that exhibited partial resistance to calcitriol [7]. The gene encoding the VDR is known to contain a number of polymorphisms. A polymorphic start codon in the 5' end of the gene is identified by the restriction enzyme *Fok*I. In the 3' end of the gene, there are 3 polymorphisms generating *Bsm*I, *Apa*I and *Taq*I restriction sites [10]. Molecular studies have shown that certain *VDR* polymorphisms could be associated with bone mineral density, hyperparathyroidism, osteomalacia, insulin-dependent diabetes mellitus, osteoarthritis, and some malignancies such as breast and prostate carcinoma [10–14]. However, a number of negative and positive associations in different populations have been reported. Genetic polymorphism of the VDR gene may influence $1,25(OH)_2D_3$-mediated normal physiologic response of keratinocytes and can explain the variable responsiveness. In this study, we aimed to compare the allele and genotype frequencies of VDR genotypes and haplotypes in psoriasis patients and healthy controls, and to determine the association between VDR polymorphism and response to vitamin D therapy.

Material and Methods

Patients

A total of 102 psoriasis patients (47 women and 55 men) and 102 controls (50 women and 52 men) were enrolled in this study. Psoriasis patients were diagnosed clinically and/or histopathologically. All the patients were clinically evaluated concerning their family history of psoriasis, nail involvement, psoriatic arthralgia, and psoriasis area and severity index. Following a 2-week wash-out period during which no systemic or topical treatments were used, 50 patients were prescribed calcipotriol ointment and/or scalp solution and asked to apply the medication over the plaques twice daily for 6 weeks. The clinical response was assessed by psoriasis area and severity index (PASI). Patients were then grouped into 2 categories: non-responders (defined as improvement less than 50%) and responders (defined as improvement more than 50%) [15].

The protocol for this study was approved by the ethics committee of the Pamukkale University, Medical Faculty. Written informed consent was obtained from all volunteers.

VDR genotype analysis

The genotype for 4 SNPs of the VDR gene was determined by the digestion pattern of the amplified DNA fragments using the restriction enzymes *Apa* I, *Bsm* I, *Fok* I and *Taq* I. Blood samples were collected into K3EDTA-tubes and stored at –20°C. DNA was extracted from whole blood by a salting out procedure [16]. Genomic DNA was amplified by PCR using specific primers as previously described: for *Apa* I and *Taq* I primer-1, 5'-CAGAGCATGGACAGGGAGCAA-3'; primer-2, 5'-GCAACTCCTCATGGCTGAGGTCTC-3' [17]; for *Bsm* I primer-3, 5'-CAACCAAGACTACAAGTACCGC GTCAGTGA-3'; primer-4, 5'-AACCAGCGGGAAGAGGTC AAGGG-3' [18]; for *Fok* I primer-5, 5'-AGCTGGCCCTGGC ACTGACTCTGCTCT-3'; primer-6, 5'-ATGGAAACACCTTG CTTCTTCTCCCTC-3' [19]. PCR was performed in a volume of 50 µl with 100 ng sample DNA, 200 µM dNTPs, 10 pmol of each primer, 1.5 mM $MgCl_2$, 1XPCR buffer and 1 U Taq DNA polymerase (MBI Fermentas, Lithuania). PCR products were amplified in a programmable thermal cycler (Hybaid-PCRSprint, Middlesex, UK). The PCR conditions were 5 min at 94°C for initial denaturation, 30 sec at 94°C, 30 sec at 60°C for *Apa* I, *Taq* I, *Fok* I, 65°C for *Bsm* I, 30 sec at 72°C, 30 cycles, followed by 5 min at 72°C for final extension. Specific PCR products were obtained 740 bp, 265 bp and 825 bp for *Apa* I and *Taq* I, *Fok* I and *Bsm* I, respectively. PCR products were digested with the restriction enzymes *Apa* I, *Taq* I, *Bsm* I (*Mva*1269I) and *Fok* I (*Bse*GI) (MBI Fermentas, Lithuania) according to the manufacturer's instructions, and electrophoresed on 1.4% or 1.7% agarose gels (Prona, Spain). For both *Bsm*I and *Fok*I, *Apa* I, and *Taq* I genotypes were defined by capital letters in the absence of the restriction site (*A, B, F, T*, respectively) and small letters where the restriction site was present (a, *b, f, t*, respectively).

Haplotype and statistical analysis

Allele frequencies were calculated from genotype frequencies based upon Hardy-Weinberg equilibrium;

p, q: allele frequency, *p2, q2, 2pq*: genotype frequency.

$$p+q=1$$
$$(p^2)+(2pq)+(q^2)=1.$$

Haplotype analysis was done by CHAPLIN1.2 [20]. Differences in the VDR allele and genotype frequency were compared between psoriasis patients and controls by significance test between percentages. One-way analysis of variance was used to compare clinical parameters with genotypes. The P value less than 0.05 was regarded as statistically significant, and analysis was carried out by SPSS9.0.

Results

Regardless of their clinical type, 102 random, unrelated Caucasian Turkish psoriasis patients (47 women, 55 men) aged 10 to 73 years (mean 44.36±16.35) and 102 unrelated, healthy Caucasian Turkish controls (50 women, 52 men) aged 15 to 75 years (mean 40.83±16.88) were included. No significance was found between mean age of female and male psoriasis patients. Of the 102 patients, 69 (67.6%) were plaque, 16 (15.7%) were plaque plus guttate, 10 (9.8%) were guttate, 5 (4.9%) were palmoplantar, and 2 (2%) were pustular palmoplantar type of psoriasis (Table 1).

Patients were grouped according to their age of onset as Type I (early onset, <40 years old) and Type II (late onset, >40years old) psoriasis. Type I psoriasis was 63.7% and Type II psoriasis was 36.3% of all patients. Mean age at onset of all patient groups was 32.33±16.76, in the early group 20.39±11.14 for women, 24.94±10.87 for men; in late group 47.47±6.45 for women, and 53.11±8.80 for men. There was no statistical significance between mean age of onset in female and male psoriasis patients. Nail involvement and arthralgia were present in 32.4% and 38.2% of patients, respectively.

In total, 50 patients received calcipotriol therapy and 1 patient was excluded because of irritation and discarded from analysis. Of the 49 patients, 31 (63.3%) had improvement less than 50% and were grouped as non-responders, and 18 (36.7%) patients had more than 50% response. We did not find any significance between response to calcipotriol therapy and sex, early and late onset of the disease, clinical type, or family history (p>0.05).

Allele frequency of T and genotype frequency of Tt was significantly higher in patients than controls (p values 0.038 and 0.04, respectively) (Table 2). The Aa and bb genotypes were significantly higher in early onset than late onset psoriasis (p values 0.008 and 0.04, respectively). The genotype Ff was significantly higher in non-responders, while ff and TT were significantly lower in non-responders to the vitamin D_3 therapy (p values 0.04, 0.0001, 0.009, respectively).

This is the first report of importance a VDR gene haplotype in psoriasis (the significance of the Wald and LR statistics p=0.0042), suggesting that FfBbAatt is a disease-susceptibility haplotype.

Discussion

The data related to VDR polymorphisms and psoriasis is very limited in the literature when compared with other situations such as bone mineral density, diabetes and cancers.

Lee et al. in 2012 [21] conducted a remarkable meta-analysis and reported that overall association has not been found, while A allele, FF and ff genotypes are ethnically important in Turkish populations and B allele only in Asians. However, Zeul-Fakkar et al in 2010 [22] reported no association with *Apa* I and *Taq* I polymorphisms in Egyptian patients.

Dayangac et al. in 2007 [23] studied 51 Turkish psoriasis patients and reported that T allele and TT genotype was higher in patients, and also higher in non-responders of vitamin D_3 therapy, in contrast to the study of Halsall et al. in 2005 [24], who reported that T allele, TT and AA genotypes are associated with response to vitamin D_3 in white Caucasian patients. However, it was reported by Giomi et al. in 2005 [25] and Holick et al. in 1996 [26] Bb and bb genotypes are associated with response to vitamin D_3 respectively. Park et al. in 1999 [27] found AA and Aa genotypes significantly higher in psoriasis patients, especially in the early onset group, and found no significance for *Bsm*I and *Taq*I polymorphisms. Mee et al. in 1998 [9] found the Aa genotype has been associated with early onset of psoriasis. Lee et al. in 2002 [28] and Kontula et al. in 1997 [29] reported there was no correlation between *Bsm* I and *Apa* I polymorphisms and clinical response.

Kaya et al. in 2002 [30] also studied 53 Turkish psoriasis vulgaris patients and reported the Aa and aa genotypes as a high risk for psoriasis vulgaris in the Turkish population. Neither this study nor Dayangac et al. in 2007 [23] have found association with Apa I polymorphism. Okiata et al. in 2002 [31] reported that AA genotype was higher in pustulosis palmaris et plantaris than in psoriasis vulgaris than in psoriasis pustulosa; however, there was no correlation between PASI score and age at onset.

In terms of haplotype, Rucevic et al. in 2012 [32] did not find any association with the 3' region of the VDR gene. Halsall et al. in 2005 [24] found a powerful correlation with combined genotypes AAFF, AATT and FFTT. The haplotypes are tags which are sum of the marker polymorphisms in a gene. Individually, SNPs and genotypes may not have significance and association, but together as haplotype they can. The haplotype we found may indicate that a special final vitamin D receptor protein is made susceptible to psoriasis by changing RNA splicing, processing and editing, or by changing receptor protein folding or changing by affinity and binding specifically to DNA response elements or other nuclear receptors, which function as hetero/homodimers or functional structures of receptors. The VDR is a regulatory protein, and its final haplotype may disrupt the regulatory function and may complement the other disturbing factors. This may be confirmed by studying interaction and activity characteristics of VDR protein in these subjects. In addition, transcriptome results, which were provided by Jordan et al. [2], can give some clues about the starting point.

Morrison et al. in 1992 [18] reported that the b allele tends to decrease VDR mRNA expression. Chen et al. in 1996 [33] reported that VDR expression has been induced in psoriatic lesion of patients who received vitamin D, indicting that vitamin D_3 induced the expression of VDR mRNA in responders but not in non-responders. They suggested that the medication played a role in regulation of epidermal keratinocytes and fibroblast proliferation, or in some other way affected lymphocyte migration and proliferation in psoriatic lesions. It is remarkable that *Apa* I polymorphisms A, and in some cases T (*Taq* I), are often reported in association with psoriasis. The mechanism of vitamin D_3 therapy and the cause of the resistance in some patients still remain unclear. The *Apa* I polymorphisms are in the intronic site of the gene, and its importance may be explained by introns playing a role in control of expression through RNA editing and alternative splicing.

Table 1. Clinical summary of the patients.

Case code	Gender	Age	Response to Vit D_3 Therapy	PASI 0	PASI 6	Response%	Psoriasis Type	Arthritis	Artralgia	Nail involvement	Age at onset	Disease duration (Years)	Family history
16	F	42	+	1	0	100	Plaque	+	+	–	41	01	+
23	F	55	+	2	0	100	Plaque	–	–	–	48	07	–
37	M	50	+	1	0	100	Plaque	–	–	–	48	02	–
49	M	33	+	1	0	100	Plaque	–	–	–	25	08	–
20	M	35	+	1	0	100	G + P	–	–	–	29	06	–
4	F	20	+	1	0	86	Plaque	–	–	+	15	05	–
25	M	19	+	1	0	50	Plaque	–	–	–	17	02	–
34	M	19	+	1	0	60	Plaque	+	+	–	05	14	+
22	M	61	+	4	1	83	G + P	–	–	+	51	10	–
11	F	37	+	2	1	65	Plaque	–	–	–	27	10	–
42	M	71	+	2	1	63	Plaque	+	+	–	61	10	–
13	M	25	+	4	1	78	Guttate	–	–	–	19	06	–
8	F	56	+	3	1	57	Plaque	–	–	–	36	20	+
36	F	21	+	2	1	50	Guttate	–	–	+	16	05	+
2	F	34	+	3	1	53	Palmoplantar	–	–	–	34	00	+
47	M	24	+	4	2	56	Plaque	–	–	–	12	12	–
28	M	44	+	4	2	50	Plaque	–	–	–	43	01	–
5	F	61	+	10	3	67	G + P	+	+	–	46	15	–
3	F	53	–	2	1	25	Plaque	+	+	–	46	07	–
24	F	41	–	2	1	25	Plaque	+	+	–	36	05	–
31	F	55	–	1	1	14	Plaque	+	+	–	54	01	–
30	M	72	–	2	2	17	Plaque	–	+	+	66	06	–
15	F	38	–	1	2	–23	Plaque	+	+	+	28	10	–
17	F	65	–	2	2	00	Plaque	–	–	+	40	25	–
21	M	70	–	2	2	27	Plaque	+	+	–	40	30	+
33	F	42	–	3	2	43	Plaque	–	–	–	30	12	+
10	F	48	–	1	2	–14	Palmoplantar	+	+	+	43	05	–
45	M	50	–	2	2	17	Plaque	–	–	–	40	10	–
14	F	44	–	2	2	17	Palmoplantar	–	–	–	43	01	–
46	M	50	–	2	2	17	Palmoplantar	–	–	–	40	10	–
19	F	38	–	3	2	29	Plaque	+	+	–	06	32	+
12	F	10	–	2	2	–35	Plaque	–	–	–	05	05	–
27	F	33	–	4	3	32	G + P	–	–	+	18	15	–
38	M	47	–	2	3	–17	Plaque	–	–	–	27	20	–
1	M	50	–	4	4	00	Plaque	–	–	–	40	10	–
40	F	45	–	7	4	45	Guttate	–	–	–	44	01	–

Table 1 continued. Clinical summary of the patients.

Case code	Gender	Age	Response to Vit D_3 Therapy	PASI 0	PASI 6	Response%	Psoriasis Type	Arthritis	Artralgia	Nail involvement	Age at onset	Disease duration (Years)	Family history
41	F	20	–	4	4	02	Plaque	–	–	–	05	15	+
29	M	23	–	4	4	–10	G + P	–	–	+	13	10	+
48	M	30	–	4	5	–24	Plaque	–	–	–	29	01	+
18	F	63	–	5	5	02	Plaque	+	+	+	54	09	–
39	M	45	–	7	5	30	Plaque	+	+	–	35	10	–
26	M	63	–	3	5	–71	Plaque	–	–	+	63	00	–
44	F	68	–	6	5	17	Plaque	+	+	–	58	10	–
35	M	65	–	8	5	33	G + P	–	–	–	35	30	+
7	F	48	–	8	6	24	Plaque	+	+	–	32	16	–
6	M	70	–	8	6	21	Plaque	+	+	+	45	25	+
32	M	48	–	10	7	28	G + P	+	+	–	28	20	–
43	M	52	–	7	8	–18	Plaque	–	–	+	50	02	+
9	M	33	–	4	8	–131	Plaque	–	–	+	23	10	–

PASI 0 – PASI (severity index) score at the beginning of the Vit D_3 therapy; PASI 6 – PASI (severity index) score at the end of the Vit D_3 therapy; G + P: Guttate and Plaque.

Table 2. Statistically significant polymorphisms.

Allele/ genotype	Frequency %		P Value
	Patients	Controls	
T (p)*	37%	43%	0.03
Tt (2pq)**	46%	32%	0.04
	Responder	Nonresponder	
Ff (2pq)***	14%	42%	0.04
ff (q^2)***	11%	8%	0.0001
TT (p^2)***	8%	4%	0.009

* Allele frequencies (p and q) of patients and controls. ** Genotype frequencies (p^2, q^2 and 2pq) of patients and controls. *** Genotype frequencies of vitamin D therapy responders and nonresponders.

In conclusion, the findings indicate that VDR polymorphisms may affect response to vitamin D_3 therapy and onset of psoriasis.

Conclusions

The number of markers used for genetic association studies are increasing rapidly. After the SNPs era, the copy number variations became very popular and useful in these days, as well junk DNA imminent will become. Genotype analysis has been used for a long time. However, haplotype analysis has recently become important due to the newly developed bioinformatics packets. Every haplotype can be used for creation of haploblocks and tagging. In the view of VDR and psoriasis, only 2 haplotypes were found, including this study. We believe that every association found makes great contribution to our understanding of the resistance to vitamin D_3 therapy in psoriasis. These data can be clarified by the structure-function and binding characteristics studies of the related VDR protein.

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