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The CDX2 G allele and the FoKI F allele of the VDR gene are more prevalent and related to changes in vitamin D levels in patients with psoriasis vulgaris: A pilot study

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Abstract

Background and aims: Psoriasis is a chronic, non-contagious autoimmune condition marked by dry, itchy,erythematous and scaly plaques. From modest, localized plaques to total body coverage, the severity of psoriasis varies. Plaque, guttate, inverted, pustular, and erythrodermic psoriasis are the five primary kinds. About 90% of cases are of plaque psoriasis, commonly known as psoriasis vulgaris. Study aims to determine the impact of an rs2228570 (FokI) variant and an rs11568820 (CDX2) variant on serum vitamin D levels (SVD) in patients with psoriasis, and the correlation between the two variants and disease severity.

Methods: A case-control study consisting of 95 psoriasis vulgaris patients and 84 healthy controls. The clinical investigation, molecular genetics analysis, and biochemical analysis were done for both groups.

Results: SVD levels were significantly decreased in psoriasis patients group. FokI genotypes analysis, we found no significant variance between groups. CDX2 G/G genotype is more prevalent in patients than controls. Moderate psoriasis vulgaris patients with CDX2 G/G genotypes have higher SVD levels than CDX2 G/A, and CDX2 A/A $p = 0.003$.

Conclusion: The study found a difference in vitamin D levels between patients and healthy subjects, as well as a difference in vitamin D levels with different FoKI and CDX2 genotypes.

KEYWORDS
CDX2, FokI, psoriasis vulgaris, vitamin D

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BSA, body surface area; BSA, body surface area; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; sVDLs, serum vitamin D levels; VDR, vitamin D receptor; Vitamin D3, (cholecalciferol).

1 | INTRODUCTION

Psoriasis is one of chronic, inflammatory autoimmune skin aliment influenced by environmental and genetic factors. It has been identified as a significant public health burden, affecting an estimated more than 120 million, or near to 5% of the population. Although psoriasis has a low mortality rate, patients with the disease experience significant impairment in life quality and a significant psychosocial burden.[1,2]

Psoriasis tends to affect both men and women, with no preference for one over the other[3] and its clinical lesions develop between the ages of 20 and 30. However, children and adolescents may also be affected.[4,5]

Vitamin D D3(1,25(OH)2D3) is thought to be an immune system control board. Vitamin D activity is dependent on the vitamin D receptor (VDR), a descendant of the nuclear hormone receptor family. The VDR gene can be found on chromosome 12q13.11[6] and has several polymorphisms that correlate with other aliments as bronchial asthma, eczema, and psoriasis.[7–12]

VDR genes FoKI and CDX2 polymorphisms have a role in the etiopathogenesis of psoriasis, it could considered as a marker or have a role in developing a management plan.[7–12]

Previously, we examined TaqI[13] and ApaI.[14] This study carried on to ascertain how other variations in the VDR genes FoKI and CDX2 affect the chance of developing psoriasis. This study aims to determine the impact of an rs2228570 (FoKI) variant in coding areas and an rs11568820 (CDX2) variant in the promoter region in blood 25(OH)D) concentration in patients with psoriasis, as well as whether there is any correlation between them and severity of the disease.

2 | SUBJECTS AND METHOD

2.1 | Subjects

This case-control study was conducted at the dermatological clinic in one year. It was carried out in conformity with the Helsinki Declaration guidelines and was certified by the Regional Ethical Committee. Prior to enlistment, all participants signed a written consent form after being briefed on the purpose and scope of the investigation. Affected individuals of any age or gender with a definitive diagnosis of psoriasis but no multisystem involvement were eligible to participate. Individuals on vitamin D therapy, pregnant women, nursing mothers, cancer patients, and those with active liver or renal disease were all excluded.

The study enrolled 95 psoriasis patients (49 men and 46 women) as there are other 84 participants as control, and the diagnosis was determined through medical and physical assessment as the disease progressed (all patients had characteristic erythematous-squamous plaques located on the trunk and limbs). Patients with severe psoriasis vulgaris (more than 10% of the body surface), moderate psoriasis vulgaris (5%–10% of the body surface), and mild psoriasis vulgaris (less than 5% of the body surface) were separated into three categories.[15]

As a "feasibility" study, we carried out a pilot study with a small number of subjects. This is a small-scale preliminary report commissioned prior to large-scale quantitative research to assess the feasibility of a future study that examined the FoKI polymorphism and cdx2 and there correlation with psoriasis severity. Before embarking on a full-scale project, we can forecast an adequate sample size, expenditure for it, and enhance the study design.

The remaining 84 participants were healthy volunteers of the psoriasis cluster's age and gender (48 males and 36 females); they showed no clinical signs of psoriasis or any other autoimmune disorder. Both clusters received comprehensive physical and medical analyses, genotyping, and vitamin D esteems.

3 | GENOTYPES ANALYSIS

3.1 | DNA extraction and PCR-RFLP analysis

Anticoagulant Na2EDTA was used to gather blood samples. The QIAamp DNA Blood Mini Kit was used to purify genetic DNA from 200 μL of whole blood based on the manufacturer's Blood protocol directions (Qiagen, Hilden, Germany).

3.2 | Genotypes analysis for FoKI variants

The extracted DNA was used to amplify the target sequences of rs2228570 FoKI gene polymorphism, the primer sequence, and the PCR and RFLP condition described by Peng and his colleagues.[16] Sequence alignment analysis was used to confirm the results by running samples on 1.5% agarose gels. The bands of the predicted size were cut, and purification was performed using the gel extraction kit according to the manufacturer's protocol (QIA quick columns, Qiagen). Purified samples were cycle sequenced with the Big Dye Terminator v3.1 Kit and injected into the ABI 3100 Genetic Analyzer (Applied Biosystems, Germany). The PCR products analyzed by sequencer were blasted to the gene bank database at https://WWW.blast.ncbi.nlm.nih.gov/Blast.cgi.

3.3 | Genotypes analysis for CDX2 variants

CDX2. VDR The tetraprimer amplification refractory mutation system PCR (T-ARMS-PCR) was constructed with two sets of primers. These allele-specific primers are G-Rev and A-For. These four primers produce three PCR products: the G-For and G-Rev primer set amplifies the G allele specifically with a fragment size of 110 bp, the A-For, and A-Rev primer set amplifies the A allele specifically with a fragment size of 235 bp, and the out primer pair (G-For and A-Rev) amplifies the internal control PCR fragment with a fragment size of 297 bp.[17]

TABLE 1 Clinical and general data characteristics of psoriatic patients and healthy subjects.

Parameters	Patients *N* (95) Mean ± SD	Healthy subjects *N* (84) Mean ± SD	*p*-value
Age	39.4 ± 2.8	32.5 ± 3.6	0.998
Male (*N*, %)	49 (51.5%)	48 (57.2%)	0.765
Female (*N*, %)	46 (48.5%)	36 (42.8%)	0.842
Severe psoriasis vulgaris (*N*, %)	35 (36.8%)	–––	NA
Moderate psoriasis vulgaris (*N*, %)	30 (31.6%)	–––	NA
Mild psoriasis vulgaris (*N*, %)	30 (31.6%)	–––	NA
Presence of family history (N, %)	56 (59%)	–––	NA
Absent of family history (*N*, %)	39 (41%)	–––	NA
Serum vitamin D level (ng/mL)	15.4 ± 5.9	28.4 ± 8.5*	0.001

Note: high significant differences ($p \leq 0.01$).
Abbreviations: N, number, NA: not applied; SD, standard deviation; %, percentage

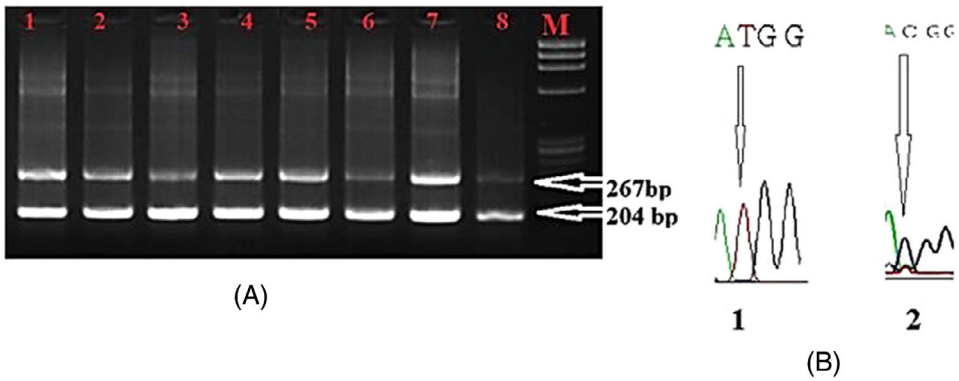

FIGURE 1 (A) Lanes from 1 to 8 restriction enzyme analysis for rs2228570 the product appears at 267 bp and 204 for CT (F/f genotype). Lane M phi × 174 markers. (B) Partial sequence VDR gene PCR fragment rs 2228570 polymorphism 1. Showing only T peak indicating T/T (f/f genotypes) 2. Showing only C peak indicating C/C (F/F genotypes).

3.4 | Serum vitamin D (SVD) Concentration Measurements

The patients' baseline SVD concentrations were assessed. Within 24 hours, samples of blood were taken from veins and evaluated using the Roche Cobas e411 (Roche Diagnostics System, Switzerland). The Institute of Medicine's Food and Nutrition Board classed SVD levels as adequate (> 20 ng/mL), insufficient (12-20 ng/mL), or defective (12 ng/mL).[18]

3.5 | Statistical analysis

UsingSN Pstats (http://bioinfo.iconcologia.net/SNPstats) and the Arlequin software (version 3.1), allele frequency, genotypes, and Hardy-Weinberg equilibrium was calculated. If $p \geq 0.05$, the Hardy-Weinberg equilibrium is considered significant. The statistical package for social science (SPSS) software version 20 was used to analyze the data (Chicago, IL, USA). The mean and standard deviation (SD) expressed every numerical variable. We were comparing qualitative data involved using the chi-square test. An analysis of variance (ANOVA) test with one way was used to compare three variables. The cutoff for statistical significance was $p \leq 0.05$.

4 | RESULTS

4.1 | General information regarding both patients and controls

Table 1 shows medical and general information for individuals and the other group. Compared to the patient's group, vitamin D levels were significantly greater in the healthy group ($P = 0.001$). We used PCR to amplify a particular region of the rs2228570 FokI gene polymorphism, then RFLP and sequencing analysis to determine the genotypes (Figures 1A and 1B). The results of an ARMS study of rs11568820 CDX2 genotypes are displayed in (Figure 2).

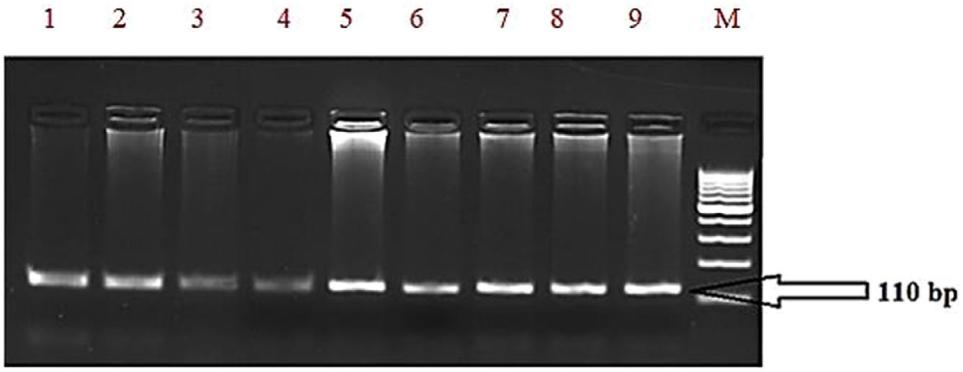

FIGURE 2 Lanes from 1 to 9 ARMS analysis for CDX2 variant the product appear at 110 bp G/G genotypes. Lane M (100 bp DNA Marker).

4.2 | Alleles frequency and genotypes for psoriatic patients and healthy subjects

With a *p*-value of 0.66, CDX2 variant patients and controls genotype distribution was in Hardy-Weinberg equilibrium. In contrast, the genotype distribution of patients and controls for FoKI was 0.023 and 0.38, respectively.

Using the co-dominant, dominant, and receive models to compare the genotypes of rs 2228570 in patients and healthy participants, we found no significant variance between groups Table 2A. Additionally, there were no notable differences between patients and controls in the allele frequency Table 2B.

The most prevalent CDX2 genotype among patients (37.9%) was G/G. In the co-dominant model, the (G/A) and (A/A) were respectively the most prevalent in healthy subjects (52.4%) and (30.9%). In the dominant model, (G/G) is quite common in individuals than control participants (G/A-A/A). While (G/G-G/A) is more prevalent in patients with the recessive model and (A/A) is more prevalent in controls Table 2A.

In CDX2 variants, the results have shown that the (G) allele was over-represented in patients compared to healthy subjects (63% vs. 43%) with considerable distinctions of $p = 0.003$. Also, there are considerable distinctions between patients and healthy subjects in the (A) allele (37% vs. 57%) ($p = 0.002$) Table 2B.

4.3 | Compare the alternation in vitamin D with variants of VDR variants genotypes

In the Co-dominant Model, Patients with (F/F) genotypes have statistically significantly higher SVD levels ($p = 0.004$) Table 3A, the same result is indicated in the dominant model where F/F genotypes have higher SVD levels than (F/f -f/f) Table 3B. No significant difference between (F/F-F/f) and (f/f) in the recessive model Table 3C. This result indicated the role of (F) allele in increasing vitamin D levels. The results of CDX2 in co- dominant model indicated that patients with G/A had higher vitamin D levels compared to G/G and A/A Table 3A. Where there is no significant difference between genotypes in the dominant model Table 3B. But the vitamin D levels were higher in genotypes (G/G-G/A) compared to A/A which focuses light on the role of the G allele of CDX2 in changing levels of vitamin D Table 3C.

4.4 | Compare the alternation in vitamin D with variants VDR variants genotypes in different clinical variants

When SVD levels were compared to various clinical forms of psoriasis, it was discovered that severe psoriatic patients had higher SVD levels than mild psoriasis and severe psoriasis vulgaris patients, with $p = 0.005$ (Table 4A).

They tried to compare the FoKI genotypes amongst the variable clinical forms, showing that SVD levels were no significant variation in severe, moderate, and mild (Table 4B-D). The same results were observed in CDX2 genotypes in severe and mild with P values 0.461 and 0.911, respectively (Table 4B and 4D). While in moderate patients, CDX2 G/G have higher vitamin D levels than CDX2 G/A and CDX2 A/A P = 0.003 (Table 4C).

5 | DISCUSSION

We concentrated on the genetic variables as a significant predictor of these disorders because psoriasis is a complex disease. Numerous genes have been investigated in this approach; one notable aspect of psoriasis is the VDR gene.[19–21] According to our knowledge, this is the first study that aims to explore and try to find the relation between FoKI and CDX2 change in SVDlevels in psoriasis and our population. We study FoKI and CDX2 for their important role in vitamin D biosynthesis because this polymorphism is located in exon 2 of the VDR gene and promoter region, respectively.

The main finding of this research is that SVD levels are much lower in psoriasis patients than in control groups. This finding matches our previous studies.[13,14] Also, Studies by Orgaz Molina et al. and Chandrasekhar et al. revealed comparable findings.[22,23] Studies conducted in India, and Nepal, showed a similar outcome.[24,25] Additionally, our

TABLE 2 Association of genetic variants in VDR gene in psoriatic patients and healthy controls.

A) Variants genotypes	Model	Patients N (%)	Healthy controls N (%)	OR (95%CI)	P- Value
FoKI rs 2228570					
F/F	P (HWE)	0.023 [b]	0.38 [b]	1.00	
F/f		33(34.7%)	23 (27.4%)	0.66 (0.33-1.33)	0.51
f/f	Co-dominant	36 (37.9%)	38 (45.2%)	0.79 (0.36-1.71)	
		26 (27.4%)	23 (27.4%)		
F/F				1.00	
F/f-f/f	Dominant	33 (34.7%)	23 (27.4%)	0.71 (0.37-1.34)	0.29
		62 (65.3%)	61 (72.6%)		
F/F-F/f				1.00	
f/f	Recessive	61 (72.6%)	69 (72.6%)	1.00 (0.52-1.93)	0.998
		23 (27.4%)	26 (27.4%)		
CDX2 rs11568820					
G/G	P (HWE)	0.66 [a]	0.66 [a]		
G/A		36 (37.9%)	14 (16.7%)	1.00	
A/A	Co-dominant	47 (49.5%)	44 (52.4%)	0.42 (0.20-0.87)	0.005 [d]
		12 (12.6%)	26 (30.9%)	0.18 (0.07-0.45)	
G/G	Dominant	36 (37.9%)	14 (16.7%)	1.00	
G/A-A/A		59 (62.1%)	70 (83.3%)	0.33 (0.16-0.67)	0.001[c]
G/G-G/A		83 (87.4%)	58 (69%)	1.00	
A/A	Recessive	12 (12.6%)	26(30.9%)	0.32 (0.15-0.69)	0.002[d]
B) Allele frequency	**Patients N (%)**		**Healthy controls N (%)**		**P- Value**
FoKI					
F	102(54%)		84(50%)		0.876
f	88(46%)		84(50%)		0.657
CDX2					
G	119(63%)		72(43%)		0.003 [d]
A	71(37%)		96(57%)		0.002 [d]

Abbreviations: CI, confidence interval; HWE, Hardy-Weinberg equilibrium; OR, odds ratio.
[a]Significant with Hardy-Weinberg equilibrium.
[b]Not significant with Hardy-Weinberg equilibrium.
[c]Highly significant.
[d]significant, %: percentage, rs: Reference SNP cluster ID.

findings were consistent with the other research, which demonstrated lower serum levels of 25-hydroxyvitamin D in psoriasis patients than in control.[26–28] In contrast to what we have observed, some studies have not shown any link between 25-hydroxy vitamin D levels and the risk of developing psoriasis.[29]

The important role of vitamin D in psoriasis vulgaris and immune modulatory function can explain by biochemical pathway, it is important to note that the active form of vitamin D, along with its corresponding receptor, plays a vital role in the regulation of various cellular activities. Specifically, this dynamic duo is responsible for effectively controlling the differentiation and proliferation of keratinocytes, which are the primary cells found in the outermost layer of the skin. Furthermore, this intricate relationship between vitamin D and its receptor also has a profound impact on the balance of the cutaneous immune system, which is crucial for maintaining a healthy and properly functioning skin barrier. Additionally, it should be highlighted that this physiological phenomenon also influences the process of apoptosis, which is essentially the programmed cell death that occurs in multicellular organisms. Interestingly, scientific research has demonstrated that the 1,25(OH)D form of vitamin D possesses noteworthy anti-proliferative effects on keratinocytes, further emphasizing the significance of this dynamic interaction.[30]

In the present study, we found a high relation between the change in vitamin D levels and the genotypes of FoKI and CDX2. Also, the genotypes of FoKI and CDX2 have an important role in our patient's

TABLE 3 Comparison of serum vitamin D level and rs 2228570 genotypes in psoriatic patients.

A. Co-dominant Model				
FoKI rs2228570 variant	**F/ F (*N* = 33)**	**F/f (*N* = 36)**	**f/f (*N* = 26)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	19.8 ± 6.6**	14.4 ± 6.3	15.01 ± 3.7	0.004**
CDX2 rs11568820 variant	**G/G (*N* = 36)**	**G/A (*N* = 47)**	**A/A (*N* = 12)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	14.9 ± 6.5	18.4 ± 5.9**	12.7 ± 2.8	0.003**
B. Dominant Model				
FoKI rs 2228570 variant	**F/ F (*N* = 33)**	**F/f and f/f (*N* = 62)**		***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	19.8 ± 6.6**	14.6 ± 5.4		0.0038**
CDX2 rs11568820 variant	**G/G (*N* = 36)**	**G/A and A/A (*N* = 59)**		***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	14.9 ± 6.5	15.6 ± 5.6		0.769
C. Recessive Model				
FoKI rs 2228570 variant	**F/ F and F/f (*N* = 69)**		**f/f (*N* = 26)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	17.1 ± 6.45		15.01 ± 3.7	0.698
CDX2 rs11568820 variant	**G/G and G/A (*N* = 83)**		**A/A (*N* = 12)**	**P-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	16.65 ± 6.2**		12.7 ± 2.8	0.005**

Abbreviations: *N*, number; SD, standard deviation.
**significant differences ($p \leq 0.05$), rs: Reference SNP cluster ID.

TABLE 4 Comparison of serum vitamin D level and variable clinical types of psoriasis in our patients.

A. Variable clinical types of psoriasis				
Parameters	**Severe psoriasis vulgaris (*N* = 35)**	**Moderate psoriasis vulgaris (*N* = 30)**	**Mild psoriasis vulgaris (*N* = 30)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	18.5 ± 5.9**	14.6 ± 6.8	14.7 ± 3.8	0.005 **
B. Sever psoriasis vulgaris				
FoKI rs 2228570 variant	**F/ F (*N* = 33)**	**F/f (*N* = 2)**	**f/f (*N* = 0)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	19.7 ± 6.6	17 ± 4.6	NP	0.541
CDX2 rs11568820 variant	**G/G (*N* = 2)**	**G/A (*N* = 31)**	**A/A (*N* = 2)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	18.8 ± 4.9	19.8 ± 6.4	16.8 ± 6.7	0.461
C. Moderate psoriasis vulgaris				
FoKI rs 2228570 variant	**F/ F (*N* = 0)**	**F/f (*N* = 30)**	**f/f (*N* = 0)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	NP	14.6	NP	NA
CDX2 rs11568820 variant	**G/G (*N* = 21)**	**G/A (*N* = 0)**	**A/A (*N* = 9)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	16.9 ± 7.8**	NP	12.3 ± 3.05	0.003**
D. Mild psoriasis vulgaris				
FoKI rs 2228570 variant	**F/ F (*N* = 0)**	**F/f (*N* = 4)**	**f/f (*N* = 26)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	NP	13.2 ± 2.5	15.01 ± 3.7	0.366
CDX2 rs11568820 variant	**G/G (*N* = 12)**	**G/A (*N* = 16)**	**A/A (*N* = 2)**	***p*-Value**
Serum vitamin D level (ng/mL) (mean ± SD)	14.77 ± 3.6	15.09 ± 3.4	12.2 ± 3.9	0.911

Abbreviatins: N, number; NA, not applicable; NP, not present; SD, Stander deviation.
**Significant differences ($p \leq 0.05$), rs: Reference SNP cluster ID.

disease severity. Several researchs on VDR polymorphisms have been found. They support our point of view on the important role of VDR polymorphism and its relation to psoriasis severity.[12,19–21,31–37]

Our results shed light on the genetic impact of FoKI and CDX2 in alternating the SVD levels in our patients. Our results were conducted with many researchs.[19-21,38,39]

In the present study, we observed that our patients (F) allele of FoKI was more abundant in patients than healthy subjects. Our results are in the same line with several studies.[6,12,19,33]

Also, (G) allele of CDX2 variant is more frequent in patients than in healthy subjects. Our results match Torkko and his colleagues; they found that G allele is most frequent in Hispanic Whites (65.7 %).[40]

The results of this study revealed that G/G genotype of CDX2 is associated with elevated SVDlevels in moderate patients. This data indicates the role of CDX2, especially in the change in vitamin D levels; this may be for its position in the promoter region.

The transcriptional level of VDR mRNA is closely correlated to psoriasis patients' reaction to the antiproliferative impact of vitamin D3.[41,42] So, we can expect that patients with the (F) allele or (G) allele or both may be resistant to calcipotriol therapies, but this expectation needs to be studied.

6 | CONCLUSION

The researchers discovered a difference in SVD levels among patients and healthy individuals, as well as between different FoKI and CDX2 genotypes.

7 | LIMITATION

The limited number of patients in this research means that it does not encompass all of Saudi Arabia. Furthermore, we advise that you look into other VDR polymorphism genotypes.

AUTHOR CONTRIBUTIONS

Ahmed Ibrahim AbdElneam, Mohammed Saleh Al-Dhubaibi, Mohammad Arshad, and Saleh Salem Bahaj collect the materials. Ahmed Ibrahim AbdElneam, Mohammed Saleh Al-Dhubaibi, Saleh Salem Bahaj, Mohammed Saleh Al-Dhubaibi, Ghada Farouk Mohammed and Lina Mohamed Atef do the analysis and write the paper. Ahmed Ibrahim AbdElneam, Mohammed Saleh Al-Dhubaibi, Saleh Salem Bahaj, Mohammed Saleh Al-Dhubaibi, Ghada Farouk Mohammed and Lina Mohamed Atef wrote the manuscript. Ahmed Ibrahim AbdElneam, do the figure. Ahmed Ibrahim AbdElneam, Mohammed Saleh Al-Dhubaibi, Saleh Salem Bahaj, Mohammad Arshad, Ghada Farouk Mohammed and Lina Mohamed Atef do the tables.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

Institutional review board and Research Ethical Committee in accordance with the Helsinki Declaration guidelines.

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