

# Association of rs1544410 and rs7975232 Polymorphisms and Serum Vitamin D Levels with Psoriasis Susceptibility and Severity: A Case–Control Study in Egyptian Patients

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**Background:** Vitamin D is a regulatory factor for skin immune functions through vitamin D receptor, which is expressed on many immune cells. Vitamin D receptor is located on chromosome 12q 13.11 and has many single nucleotide polymorphisms. Some of them were hypothesized to be associated with psoriasis. Psoriasis is a genetic disease that is greatly affected by environmental factors.

**Methods:** A total of 135 psoriasis patients and 114 healthy controls were recruited. Both had a measurement of serum vitamin D and two vitamin D receptor variants: rs1544410: G > A (HGVS:NC\_000012.12:g.47846052) and rs7975232: C > A (HGVS:NC\_000012.12:g.47845054). We assessed the relationship between vitamin deficiency as well as the two gene polymorphisms with psoriasis susceptibility and severity.

**Results:** Serum vitamin D levels were not significantly different between cases and controls. However, a significant association between vitamin D levels and severity was observed. We attributed this to our finding that rs7975232 was more significantly polymorphic among cases than controls, while rs1544410 polymorphism did not show a significant difference among the 2 groups.

**Conclusion:** We did not find a significant difference in serum vitamin D levels between cases and controls. Yet, psoriasis severity was significantly associated with serum vitamin D levels. We attributed this to other findings that the vitamin D receptor rs7975232 gene is polymorphic in psoriasis patients. At the same time, rs1544410 was not significantly more polymorphic in psoriasis patients. Both genes' polymorphisms were associated with severe psoriasis.

**Keywords:** vitamin D deficiency, vitamin D receptors polymorphisms, single nucleotide polymorphism, ApaI, BsmI, rs7975232, rs1544410, psoriasis

## Background

Skin immune cells are capable of both synthesizing and responding to vitamin D,<sup>1</sup> through the expression of vitamin D receptor (VDR).<sup>2</sup> VDR is expressed by both innate and humoral immunity cells, which can explain the role of vitamin D in suppressing inflammatory cytokines.<sup>3–5</sup> Many vitamin D receptor polymorphisms have been previously reported.

Single Nucleotide Polymorphisms (SNP) in intron 8 are particularly implicated in autoimmunity. This can affect the vitamin D, VDR signaling pathway, and diminish the vitamin D effect on immune cells.<sup>6</sup>

Psoriasis is a polygenic multifactorial cutaneous autoimmune chronic disease with altered immune cell functions and cytokines.<sup>7</sup> The association between serum vitamin D levels and the presence of psoriasis as well as psoriasis severity has been studied intensively for the last decades, and the evidence is widely controversial.<sup>8,9</sup> Receptor gene polymorphisms that hypothetically explain such variable outcomes were studied among different populations and ethnicities and showed variable associations with psoriasis and psoriasis severity.<sup>10</sup> The most studied polymorphisms in psoriasis were four SNPs. They are located at exon 2 (rs2228570: C > T, detected with the FokI restriction enzyme); exon 9 (rs731236: T > C, detected with the TaqI restriction enzyme), and two SNPs on intron 8 (rs1544410:G > A, detected with the BsmI restriction enzyme and rs7975232:C > A (HGVS: NC\_000012.12:g.47845054), detected with the ApaI restriction enzymes).<sup>11</sup>

Because of these widely variable findings from the previous studies, this study was designed to investigate the association among serum vitamin D levels and the severity of psoriasis. Moreover, we aimed to detect association with two VDR receptor single-nucleotide polymorphisms located at intron 8, and these are rs7975232: C > A (HGVS: NC\_000012.12:g.47845054), detected with ApaI restriction enzymes, and rs1544410: G > A (HGVS:NC\_000012.12:g.47846052) detected with the BsmI restriction enzyme.

## Materials and Methods

### Selection of Participants

This study was conducted in the Dermatology Department, Badr University hospital, Helwan University. A total of 135 patients with psoriasis vulgaris were collected. Alongside, 115 sex-matched healthy controls were recruited. The study was approved by the Helwan University, Faculty of Medicine ethical committee and fulfilled all the ethical aspects required in human research that complies with the declaration of Helsinki. All participants received full information about the study objectives, and they all provided informed consent. We excluded patients who had any systemic treatment or phototherapy less than 6 months prior to enrollment, women who are pregnant or breastfeeding, any participant who is genetically related to another participant within the studied groups, patients that were diagnosed with any concomitant dermatological disease and individuals with prior vitamin D supplementations and any healthy controls who reported positive family history of psoriasis. All participants underwent complete history taking and full examination, and psoriasis severity was determined using Psoriasis Area and Severity Index (PASI) score.<sup>12</sup>

### Anthropometric Measurements

We measured the weight and height, then we calculated body mass index (BMI) as body weight (kg)/height<sup>2</sup> (m<sup>2</sup>), and calculated BMI Z scores online.<sup>13</sup>

### Blood Samples

A 10 mL venous sample was drawn. About 4 mL was taken in coagulant-free sterile tubes to be used in the analysis of biochemical markers. About 3 mL was taken in EDTA tubes for complete blood count (CBC) and 3 mL for DNA extraction and gene polymorphism analysis. Samples were centrifuged for coagulation, and serum was obtained immediately and stored at -80° to determine serum Vit. D by ELIZA ELISA, according to the manufacturer's instructions.

### Routine Biochemical Analysis

Glucose, Creatinine, Cholesterol, and Triglycerides were performed by an automatic autoanalyzer.

### Genetic Analysis of SNPs

Human Genomic DNA Extraction: It was carried out using QIA amp<sup>®</sup> DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany), according to recommended instructions. We measured the concentration of the extracted DNA using the Nano

Drop<sup>®</sup> (ND-1000) Spectrophotometer (Nano Drop Technologies Inc., Washington, USA). The ratio of DNA extracted absorbance was 1.7–1.9 at 260 /280 nm.

VDR rs1544410:  $G > A$  and rs7975232:  $C > A$ , SNPs polymorphism: Genotyping of VDR rs1544410,  $G > A$  and rs7975232,  $C > A$ , SNPs were carried out using real-time polymerase chain reaction with TaqMan<sup>®</sup> allelic discrimination assay software using (Applied Biosystems Step One TM Real-Time PCR system Thermal Cycling Block, Singapore), and according to the manufacturer instructions using dual-labeled fluorogenic TaqMan<sup>®</sup> probes.

## Statistical Analysis

Data were statistically described as mean±standard deviation ( $\pm$  SD), median and range, or frequencies (number of cases) and percentages when appropriate. Because the groups are large enough, a comparison of numerical variables between the study groups was performed using the Student's *t*-test for independence. For comparing categorical data, Chi-square ( $\chi^2$ ) test was performed. The exact test was used instead when the expected frequency was less than 5. Correlation between various variables was conducted using Pearson moment correlation equation for linear relation of normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. Multivariate linear regression analysis was used to test the association between vitamin D level and severity after adjusting the effect of age and gender. Two-sided *p*-values less than 0.05 were considered statistically significant. All statistical calculations were carried out by the computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA), release 22 for Microsoft Windows.

## Results

### Demographics Clinical and Laboratory Characteristics

The present study was conducted on 135 patients with psoriasis vulgaris, and 116 healthy sex-matched ( $p= 0.924$ ) controls who were slightly older than the cases ( $p= 0.000$ ). We summarized all participants' demographic, clinical, and laboratory characteristics in Table 1. There was no statistically significant difference between cases and controls regarding serum vitamin D levels ( $P= 0.161$ ), and this applied to all subgroups of vitamin D levels (sufficient, insufficient, and deficient). Vitamin D deficiency was present in 35.6% of cases vs 32.8% of controls ( $p<0.200$ ). There was no significant difference between cases and controls in CRP levels ( $p= 0.161$ ).

Among the cases with psoriasis, the prevalence of mild, moderate, and severe conditions was 18.5%, 33.3%, and 48.1%, respectively. The vitamin D level decreased with increasing severity of psoriasis (95% CI  $-0.021- -0.007$ ,  $p= 0.000$ ). No significant association was found between severity and sex or age ( $p= 543$  and  $230$ , respectively).

### rs1544410 and rs7975232 Genes Polymorphisms

Allele frequencies of rs7975232C>T (HGVS: NC\_000012.12:g.47845054) and rs1544410  $G > A$  (HGVS: NC\_000012.12:g.47846052) genotypes are shown in Tables 2 and 4. The absence of ApaI and BsmI restriction sites was described as C and G, respectively. At the same time, T and A were used to describe the presence of the sites (polymorphism), with CC and GG considered the wild type where restriction sites are absent on both alleles, CT and GA were the heterozygotic genotypes with restriction sites present on only one allele, and TT and AA were the mutant types with the presence of restriction sites on both alleles. A statistically significant difference was found among genotype frequencies between psoriasis patients and healthy controls for rs7975232C>T (HGVS: NC\_000012.12:g.47845054) and rs1544410  $G > A$  (HGVS:NC\_000012.12:g.47846052) sites where  $p= 0.001$  and  $0.002$ , respectively. However, the significance was lost after Bonferroni's adjustment (Tables 3 and 5).

rs7975232C>T (HGVS: NC\_000012.12:g.47845054) was polymorphic in 89 (65%) of cases compared to 56 (48.5%) healthy controls, and this was statistically significant ( $p= 0.005$ ). Genotype CT was the highest among psoriasis cases compared to the wild genotype CC, which was the highest among controls, and this too was also statistically significant ( $p= 0.001$ ). While rs1544410  $G > A$  (HGVS:NC\_000012.12:g.47846052) was polymorphic in 77 (57%) cases compared to 66 controls (56.9%), and this was not statistically significant ( $p= 0.982$ ). The frequency of genotype AA was significantly higher in cases than in controls ( $p= 0.002$ ).

**Table 1** Baseline Demographic, Clinical, and Laboratory Characteristics of Cases and Controls

		Controls	Cases	P value	95% Confidence Interval of the Difference	
					Upper	Lower
Gender	Male (total 96)	44 (45.8%)	52 (54.2)	0.924		
	Female (total 155)	72 (46.5%)	83 (53.5%)			
Age	Mean $\pm$ SD	54.78 $\pm$ 10.39	43.57 $\pm$ 16.922	0.000	-14.775	-7.653
	Range	17-80	15-80			
Psoriasis	None	116	0			
	Mild	0	25 (18.5%)			
	Moderate	0	45 (33.3%)			
	Severe	0	65 (48.1%)			
CRP	Mean $\pm$ SD	5.36 $\pm$ 3.303	18.31 $\pm$ 12.082	0.000		
	Range	0-18	1-56			
Vitamin D	Mean $\pm$ SD	31.09 $\pm$ 19.632	27.81 $\pm$ 17.435	0.161	-7.896	1.321
	Range	6-90	7-80			
	Sufficient (92)	49 (42.2%)	43 (31.9%)	0.200		
	Insufficient (73)	29 (25%)	44 (32.6%)			
	Deficient (86)	38 (32.8%)	48 (35.6%)			
Glucose	Mean $\pm$ SD	98.05 $\pm$ 14.536	105.06 $\pm$ 14.295	0.000	3.415	10.600
	Range	60-160	79-180			
Cholesterol	Mean $\pm$ SD	168.90 $\pm$ 28.733	195.01 $\pm$ 25.189	0.000	19.407	19.407
	Range	100-260	160-270			
Triglycerides	Mean $\pm$ SD	164.97 $\pm$ 36.555	189.48 $\pm$ 35.463	0.000	15.538	33.477
	Range	87-280	87.300			
BMI	Mean $\pm$ SD	29.06 $\pm$ 5.563	26.50 $\pm$ 3.816	0.000	-3.730	-1.384
	Range	20-40	21-40			
Creatinine	Mean $\pm$ SD	0.97 $\pm$ 0.222	0.94 $\pm$ 0.339	0.420		
	Range	0-2	0-2			

Within the psoriasis cases, rs7975232C>T (HGVS: NC\_000012.12:g.47845054) was polymorphic in 38 (42.7%) cases with deficient vitamin D, 29 (32.6%) insufficient, and 22 (24.7%) cases with sufficient vitamin D, which was statistically significant ( $p=0.019$ ). Genotype CT was also the most prevalent among the vitamin D deficient group, which was also statistically significant ( $p=0.038$ ). Rs1544410 G > A (HGVS:NC\_000012.12:g.47846052) was polymorphic in 29 (37.7%) cases with deficient vitamin D, 25 (32.5%) insufficient, and 23 (29.9%) cases with sufficient vitamin D, and this was not statistically significant ( $p=0.800$ ). Genotype GG was the most prevalent among the vitamin D deficient group, which was not statistically significant ( $p=0.965$ ) (Tables 6 and 7).

**Table 2** Comparison Between the Two Studied Groups Regarding rs 7975232 Gene Polymorphism

	Controls	Cases	P value		
				Upper	Lower
No polymorphism	60 (56.6%)	46 (34.1%)	0.005	-13.793	-1.498
Polymorphism	56 (48.3%)	89 (65.9%)			
CC	60 (51.7%)	46 (34.4%)	0.001		
CT	48 (41.4%)	59 (43.7%)			
TT	8 (6.8%)	30 (22.2%)			

**Table 3** rs 7975232 Genotypes. Bonferroni Correction for Multiple Comparisons

(I) 532 Genotype	(J) 532 Genotype	Mean Difference (I-J)	Std. Error	p value	95% Confidence Interval	
					Upper Bound	Lower Bound
CC	CT	7.611	3.379	0.078	-0.58	15.80
	TT	7.714	4.032	0.174	-2.06	17.49
CT	CC	-7.611	3.379	0.078	-15.80	0.58
	TT	0.104	3.852	1.000	-9.24	9.45
TT	CC	-7.714	4.032	0.174	-17.49	2.06
	CT	-0.104	3.852	1.000	-9.45	9.24

**Table 4** Comparison Between the Two Studied Groups Regarding rs1544410 Gene Polymorphism

	Controls	Cases	P value
No polymorphism	50 (43.1%)	58 (43%)	0.982
Polymorphism	66 (56.9%)	77 (57.0%)	
AA	10 (8.6%)	33 (24.4%)	0.002
GA	56 (48.3%)	44 (32.6%)	
GG	50 (43.1%)	58 (43%)	

### Association Between rs1544410 and rs7975232 Polymorphisms and Psoriasis Severity

Among the psoriasis patients group, polymorphic rs7975232C>T(HGVS: NC\_000012.12:g.47845054) presented in 57 of the 65 cases with severe psoriasis (87.7% of severe cases), 28 out of the 45 moderate cases (62.2% of the moderate cases), and only 4 out of the 25 mild cases (16%), which was statistically significant (p=0.000). The most prevalent genotype within moderate and severe psoriasis groups was CT, while the wild CC genotype was the most prevalent among the mild cases (84% of mild cases) (Table 8). While polymorphic rs1544410 G > A (HGVS:NC\_000012.12:g.47846052) presented in 49 of the 65 cases with severe psoriasis (75.4% of severe cases), 21 out of the 45 moderate

**Table 5** rs1544410 Genotypes After Bonferroni Correction for Multiple Comparisons

(I) 410 Genotype	(J) 410 Genotype	Mean Difference (I-J)	Std. Error	p value	95% Confidence Interval	
					Upper Bound	Lower Bound
AA	GA	-0.894	4.045	1.000	-10.70	8.91
	GG	-0.425	3.830	1.000	-9.71	8.86
GA	AA	0.894	4.045	1.000	-8.91	10.70
	GG	0.469	3.511	1.000	-8.05	8.98
GG	AA	0.425	3.830	1.000	-8.86	9.71
	GA	-0.469	3.511	1.000	-8.98	8.05

**Table 6** Association Between Vitamin D Status and rs 7975232 Gene Polymorphism in Cases with Psoriasis

Vit D Status	Cases	No Polymorphism	Polymorphism	CC	CT	TT
Sufficient	43	21 (45.7%)	22 (24.7%)	21 (45.7%)	16 (27.1%)	6 (20%)
Insufficient	44	15 (32.6%)	29 (32.6%)	15 (32.6%)	21 (35.6%)	8 (26.7%)
Deficient	48	10 (21.7%)	38 (42.7%)	10 (21.7%)	22 (37.3%)	16 (53.3%)
Total	135	46	89	46 (34.1%)	59 (43.7%)	30 (22.2%)
P value	0.019			0.038		

**Table 7** rs1544410 Gene Polymorphism in Association with Vitamin D Levels Among Psoriasis Cases

Vit D Status	Cases	No Polymorphism	Polymorphism	AA	GA	GG
Sufficient	43	20 (34.5%)	23 (29.9%)	10 (30.3%)	13 (29.5%)	20 (34.5%)
Insufficient	44	19 (32.8%)	25 (32.5%)	10 (30.3%)	15 (34.1%)	19 (32.8%)
Deficient	48	19 (32.8%)	29 (37.7%)	13 (39.4%)	16 (36.4%)	19 (32.8%)
Total	135	58 (43%)	77 (57%)	33 (24.4%)	44 (32.6%)	58 (43%)
P value	0.8			0.965		

cases (46.7% of the moderate cases), and only 7 out of the 25 mild cases (28%), which was statistically significant (p=0.000). The most prevalent genotype within severe psoriasis groups was AA (Table 9).

### Association Between Vitamin D Level and Psoriasis Severity

Vitamin D level among cases of psoriasis with rs7975232C>T (HGVS: NC\_000012.12.g.47845054) gene polymorphism ranged between 7 and 78 mg/dl, with a mean level of 25.2± 16.257, compared to its level within cases of psoriasis with no polymorphism that ranged between 8 and 80 mg/dl with mean of 32.85 ± 18.681, which was statistically significant (95% CI= -14.110- - 1.181, p= 0.021). No statistically significant difference was found between the different genotypes

**Table 8** Association Between Psoriasis Severity and rs 7975232 Gene Polymorphism

Psoriasis Severity	Cases	No Polymorphism	Polymorphism
Mild	25	21 (45.7%)	4 (4.5%)
Moderate	45	17 (37%)	28 (31.5%)
Severe	65	8 (17.4%)	57 (64%)
Total	135	46 (34.1%)	89 (65.9%)
P value	0.000		

**Table 9** Association Between Psoriasis Severity and rs1544410 Gene Polymorphism

Psoriasis Severity	Cases	No Polymorphism	Polymorphism	CC	CT	TT
Mild	25	18 (31%)	7 (9.1%)	21 (45.7%)	4 (6.8%)	0
Moderate	45	24 (41.4%)	21 (27.3%)	17 (37%)	21 (35.6%)	7 (23.3%)
Severe	65	16 (27.6)	49 (63.6%)	8 (17.4%)	34 (57.6%)	23 (76.7%)
Total	135	58 (43%)	77 (57%)			
P value	0.000					

regarding vitamin D levels ( $p = 0.053$ ). While vitamin D levels among cases of psoriasis with rs1544410 G > A (HGVS: NC\_000012.12:g.47846052) gene polymorphism ranged between 7 and 80 mg/dl, with a mean level of  $27.84 \pm 18.122$ , compared to its level within cases had psoriasis with no polymorphism that ranged between 8 and 78 mg/dl with mean of  $27.76 \pm 16.636$ , which was not statistically significant (95% CI =  $-5.933-6.104$ ,  $p = 0.978$ ). No statistically significant difference was found between the different genotypes regarding vitamin D levels ( $p = 0.975$ ).

After correction of confounders, no association was found between severity and either age or sex (95% CI =  $-0.012-0.003$ ,  $p = 0.230$ ) and (95% CI =  $-0.176-0.332$ ,  $p = 0.543$ ) respectively. However, a significant inverse relation was found between vitamin D levels and severity of psoriasis (95% CI =  $-21- -0.007$ ,  $p = 0.000$ ). Spearman correlation coefficient was  $-0.387$  and  $P = 0.000$ .

## Discussion

Although the exact pathogenesis of psoriasis is unknown, it is well established that psoriasis's genetic component plays an effective role.<sup>14,15</sup> HLA and non-HLA genes are involved.<sup>16,17</sup>

Vitamin D has a complex role in regulating skin biology, which alters keratinocytes proliferation and differentiation,<sup>18</sup> inhibits keratinocytes apoptosis,<sup>19</sup> downregulates cytokines TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8,<sup>20,21</sup> inhibits T cell proliferation and modulates T regs induction,<sup>22</sup> stimulates the expression of antimicrobial peptides,<sup>23,24</sup> and regulates barrier functions.<sup>25</sup> It has a role in several autoimmune skin disorders.<sup>26,27</sup>

In our patient's cohort, vitamin D levels showed no difference between patients with psoriasis and healthy controls. This was per several other studies.<sup>28-33</sup> On the other hand, different studies found that psoriasis patients had significantly lower serum vitamin D levels.<sup>34-37</sup> However, our patients showed a significant inverse relationship between vitamin D levels and the severity of psoriasis. Conversely, Orgaz-Molina et al and Atwa et al found a significant association between low vitamin D levels and psoriasis, but no association between vitamin D levels and psoriasis severity.<sup>34,38</sup> In contrast, other studies found a significant association between the presence of psoriasis and low levels of vitamin D, with a positive association between severity and vitamin D levels.<sup>39-41</sup>

The positive inverse association between vitamin D levels and psoriasis severity in our patients, in the absence of significant difference in serum vitamin D levels between cases and controls, can be hypothetically attributed to a polymorphic VDR gene (HGNC Id: 12679) that can affect vitamin D functions even in patients with normal serum levels. The finding supports this hypothesis that the VDR gene (HGNC Id:12679) showed decreased expression in lesional skin of psoriasis patients,<sup>42</sup> and this inverse relation was severity-dependent.<sup>43</sup> Variable evidence exists in the literature when studying different polymorphisms of VDR gene (HGNC Id:12679). The current study is concerned with intron 8 genes rs7975232C>T (HGVS: NC\_000012.12:g.47845054) and rs1544410 G > A (HGVS:NC\_000012.12:g.47846052).

Rs7975232C>T (HGVS: NC\_000012.12:g.47845054) was significantly polymorphic among our patients with psoriasis compared to healthy controls, and this was per several other studies on psoriasis patients among Turkish,<sup>44,45</sup> Korean,<sup>46</sup> and Chinese populations.<sup>47</sup> Conversely, other studies found no rs7975232C>T (HGVS: NC\_000012.12:g.47845054) polymorphism among psoriasis patients in Egyptian,<sup>48</sup> Italian,<sup>49</sup> Chinese,<sup>51</sup> Croatian,<sup>51</sup> and Japanese populations.<sup>52</sup>

The heterozygotic genotype was the most prevalent among our patients compared to the wild type that was the most prevalent among healthy controls, while in a previous Egyptian study, the heterozygotic genotype was the most prevalent among both patients and controls.<sup>48</sup> The discrepancy in results between the current study and the previous one can be attributed to the larger sample size recruited. However, the wide genetic variations among Egyptians cannot be disregarded.<sup>53</sup> Ruggiero et al suggested that the role of the VDR gene polymorphism in psoriasis can vary dramatically among different ethnic groups within the same population.<sup>54</sup> Indeed, genotypes prevalence was widely variable among different studies, even in the same populations. Results similar to ours with the prevalence of heterozygotic type among patients while the homozygotic wild type prevalent among healthy controls were previously found in studies on Turkish,<sup>44</sup> and Asian populations.<sup>55</sup> However, other studies found the prevalence of the wild homozygotic genotype in both cases and controls.<sup>47,50</sup> Heterozygotic genotype was also found prevalent in some studies,<sup>49,51</sup> while Saeki et al found prevalent mutant genotype among both cases and controls.<sup>56</sup>

There was no significant polymorphism in the rs1544410 G > A (HGVS:NC\_000012.12:g.47846052) gene among psoriasis patients in the current study. This was in accordance with several other studies among psoriasis patients in England,<sup>57</sup> Chinese,<sup>50</sup> Italian,<sup>49,54</sup> Turkish,<sup>44</sup> and Korean populations,<sup>58</sup> while unlike ours, one study found an association between rs1544410 G > A (HGVS:NC\_000012.12:g.47846052) polymorphism and psoriasis in the Japanese population.<sup>56</sup> The homozygotic polymorphic genotype in our patient's cohort was significantly higher among cases than in healthy controls. However, the heterozygotic genotype was the most prevalent among healthy controls, while the wild homozygotic type was the most prevalent among psoriasis cases. Other studies among Caucasian populations found similar results, with the prevalence of heterozygotic genotype being the most prevalent among healthy controls; however, they also found the same genotype mostly prevalent among psoriasis cases.<sup>44,51,54</sup> Conversely, studies among Asian populations found the homozygotic polymorphic genotype most prevalent among both psoriasis cases and healthy controls.<sup>52,56,58,59</sup>

In the current study, both rs7975232C>T (HGVS: NC\_000012.12:g.47845054) and rs1544410 G > A (HGVS: NC\_000012.12:g.47846052) polymorphisms were positively correlated to psoriasis severity, and there are limited data in the literature on the association between VDR gene (HGNC Id:12679) polymorphism and psoriasis severity.<sup>10,60</sup> We suggest that the wild genotype of both studied genes could be protective against the severe condition. Unlike our results, the previous study among Egyptian patients with psoriasis and another study among Turkish patients with psoriasis found no association between rs7975232C>T (HGVS: NC\_000012.12:g.47845054) VDR polymorphism and PASI.<sup>48,52</sup> Our results suggest that the wild gene in both rs7975232C>T (HGVS: NC\_000012.12:g.47845054) and rs1544410 G > A (HGVS:NC\_000012.12:g.47846052) can have a protective role against severe psoriasis cases.

The current study provided more evidence of the association between serum vitamin D levels and psoriasis and psoriasis severity and the role of VDR and its gene polymorphisms in such association. Several clinical and public health implications can be reached from these findings. It gives some insight into the potential presence of hypovitaminosis D manifestations in individuals with sufficient serum levels, as VDR gene (HGNC Id: 12679) polymorphism can affect vitamin D functions.

Our study has several methodologic and scientific strengths. We used our case-control study to estimate the prevalence of vitamin D deficiency in psoriasis patients. We adjusted for potential confounders, including age and



gender, since we did not match them at the recruitment stage. In addition, we explored effect modification by vitamin D level, age, and gender, which is not frequently performed in dermatologic research. Although we did not perform a priori formal sample size and power calculation, a closer look at the narrow confidence intervals reveals that our study was powered enough.

Our findings still need to be considered with some limitations in mind. We conducted a case-control study, so there is a potential confounding. Reverse causation is a concern in all case-control studies. There is a lack of information regarding sun exposure cases and controls. Finally, we could only assemble a small sample size which might affect statistical evaluation and conclusions.

## Conclusion

The current study found that serum vitamin D levels were not associated with psoriasis, although within the psoriasis cases, the Vitamin D levels were inversely related to severity. We attributed this to our other findings that showed an association between rs7975232C>T (HGVS: NC\_000012.12:g.47845054) gene polymorphism and the presence of psoriasis. Although rs1544410 G > A (HGVS:NC\_000012.12:g.47846052) polymorphism was not associated with the presence of psoriasis, both genes were polymorphic in severe psoriasis cases. Further studies are needed to determine the role of the VDR gene (HGNC Id: 12679) in psoriasis.

## Statement of Ethics

The ethical committee of the faculty of Medicine, Helwan University, approved this research in Oct. 2021 with serial 69/2021. Informed consent was obtained from all participants and guardians of participants less than 18-year-old. The study fulfilled all the ethical aspects required in human research.

## Disclosure

The authors report no conflicts of interest in this work.

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