Impact of vitamin D receptor gene variants on psoriasis vulgaris susceptibility and clinical phenotype in a Greek population

POLYTIMI SIDIROPOULOU[1,2], MARTHA KATSAROU[2], MARIA PAPASAVVA[2,3], ANNIA TSOLAKOU[2], AKYLAS FOTIADIS[4], DEMETRIOS A. SPANDIDOS[5], NATALIA ROMPOTI[1], IRENE STEFANAKI[1], ALEXANDER J. STRATIGOS[1], NIKOLAOS DRAKOULIS[2] and ELECTRA NICOLAIDOU[1]

[1]1st Department of Dermatology-Venereology, Medical School, National and Kapodistrian University of Athens, 'A. Sygros' Hospital for Skin and Venereal Diseases, 16121 Athens, Greece; [2]Research Group of Clinical Pharmacology and Pharmacogenomics, Faculty of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, 15771 Athens, Greece; [3]Department of Pharmacy, School of Health Sciences, Frederick University, 1036 Nicosia, Cyprus; [4]Department of Electrical and Computer Engineering, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece; [5]Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion, Greece

Received December 14, 2025; Accepted March 24, 2026

DOI: 10.3892/etm.2026.13188

Abstract. Psoriasis vulgaris (PsV) is a complex immune-mediated disease with a polygenic component. Common variants in the vitamin D receptor (VDR) gene have been explored in the context of psoriasis, but findings remain inconsistent and data from the Greek population are scarce. Thus, the present study aimed to investigate the association of the VDR FokI (rs2228570), BsmI (rs1544410) and TaqI (rs731236) single-nucleotide polymorphisms (SNPs) with PsV susceptibility and clinical phenotype in a Caucasian Greek cohort. In this observational cross-sectional study, 203 patients with chronic plaque psoriasis and 812 age-, sex- and ethnically-matched controls of Greek origin were genotyped for the selected VDR SNPs using real-time PCR (melting curve analysis) and SNP-based statistical comparisons were performed. Case-control analyses exhibited a significant association between the BsmI variant and PsV susceptibility under the recessive and allelic models, with the A allele (A vs. G; OR: 0.765; 95% CI: 0.614-0.953; adjusted P=0.032) and AA genotype (AA vs. GA + GG; OR: 0.577; 95% CI: 0.386-0.861; adjusted P=0.028) conferring a protective effect. No impact on PsV risk was observed for FokI or TaqI. Intra-patient subgroup analyses based on clinical traits indicated phenotype-specific contributions: FokI was associated with early-onset and familial disease, TaqI with psoriatic arthritis and both BsmI and TaqI with nail involvement. To the best of our knowledge, this study provides the first evidence that VDR genetic variation may influence PsV susceptibility and clinical expression in the Greek population. The VDR locus could thus serve as a potential biomarker for tailored risk stratification and clinical profiling in PsV. Further large-scale studies integrating genotypic and phenotypic data, especially among Caucasians, are required to validate these findings.

Correspondence to: Dr Polytimi Sidiropoulou, 1st Department of Dermatology-Venereology, Medical School, National and Kapodistrian University of Athens, 'A. Sygros' Hospital for Skin and Venereal Diseases, 5 I. Dragoumi Street, 16121 Athens, Greece
E-mail: sidiropouloupolytimi@gmail.com

Abbreviations: 3'-UTR, 3'-untranslated region; BSA, body surface area; FDR, false discovery rate; GWAS, genome-wide association studies; HWE, Hardy-Weinberg equilibrium; IQR, interquartile range; LD, linkage disequilibrium; OR, odds ratio; PsA, psoriatic arthritis; PsV, psoriasis vulgaris; SNP, single-nucleotide polymorphism; Th, T helper; VitD, vitamin D; VDR, vitamin D receptor

Key words: plaque psoriasis, immune-mediated skin diseases, vitamin D pathway; vitamin D receptor polymorphisms, FokI, BsmI, TaqI, genetic susceptibility, clinical features, genotype-phenotype association

Introduction

Psoriasis is an immune-mediated inflammatory disease with a global prevalence of 2-3% (1,2). Chronic plaque or psoriasis vulgaris (PsV), the most common subtype, is a multifactorial condition involving complex genetic, immunologic and environmental interactions (1,2). Genetic studies have identified numerous PsV risk loci, primarily associated with immune pathways, inflammatory cascades and epidermal homeostasis, underscoring its polygenic yet partially elucidated genetic nature (3,4).

Vitamin D (VitD) has attracted attention in psoriasis research due to its pleiotropic effects on key psoriatic elements (5-9). Recent data further support a broader cutaneous VitD-related metabolome that may influence skin homeostasis and inflammation (10). VitD promotes keratinocyte differentiation while inhibiting proliferation, thereby counteracting the epidermal hyperplasia of psoriatic plaques (5,6). It also enhances skin barrier integrity by

regulating cornified-envelope proteins, such as involucrin and loricrin, lipid synthesis and tight junction components, including claudins (5,7). Beyond its epidermal actions, VitD exerts anti-inflammatory and immunomodulatory effects, including the suppression of plasmacytoid dendritic cells (central initiators of psoriatic inflammation) and inhibition of the T helper (Th)-1/Th17 axis, downregulating associated cytokines (e.g., TNF-α, IFN-γ, IL-1, IL-2, IL-6, IL-8, IL-12, IL-17, IL-22 and IL-23) (5,6). In addition, VitD interferes with major psoriasis-related pathways, including NF-κB and JAK/STAT signaling, and also exerts anti-angiogenic activity, thereby mitigating neovascularization in psoriatic lesions (Fig. 1) (5,8,9).

Previous studies have reported a potential link between VitD deficiency and psoriasis, demonstrating inverse associations between serum VitD levels and disease risk or severity (5,11,12). In addition, altered VitD receptor (VDR) expression has been observed in psoriatic skin (5,7). From a therapeutic perspective, phototherapy, widely used in psoriasis management, may partly exert its effects by elevating serum VitD levels and/or upregulating VDR expression in lesional skin (5,13,14). Furthermore, VitD-based interventions have been shown to be beneficial in psoriasis. Although oral supplementation remains controversial across studies, topical VitD analogs are established treatment modalities (5).

Since the nuclear VDR is the main mediator of most biological actions of active 1,25-dihydroxy $VitD_3$ (5), the VDR gene has been investigated in relation to psoriasis (15). Located on chromosome 12q13.11, the VDR gene is highly polymorphic containing numerous single-nucleotide polymorphisms (SNPs) that may alter VDR expression or function (16-18). Among the most widely studied VDR variants are FokI (rs2228570; exon 2; +30920 C>T), near the start codon and BsmI (rs1544410; intron 8; + 63980 G>A) and TaqI (rs731236; exon 9; +65058 T > C) both in the 3'-untranslated region (3'-UTR) (16-18). FokI involves a T-to-C substitution that alters the translation initiation site (ATG to ACG), creating two VDR isoforms of different length (427 vs. 424 amino acids) and transcriptional capacity (17,18). The shorter isoform (associated with the C allele) is more transcriptionally active (16-19), potentially enhancing downstream VitD/VDR signaling. FokI is thus a VDR SNP that exhibits a functional impact on protein activity. By contrast, the 3'-UTR non-functional BsmI (G-to-A substitution) and TaqI (T-to-C transition) variants do not alter the protein structure but may influence VDR gene expression and protein levels by affecting mRNA stability, splicing patterns or through linkage disequilibrium (LD) with other functional polymorphisms within the VDR locus (16-19). Particularly for TaqI, its location within a CpG island, where allele-dependent methylation patterns (TT absent, TC partial and CC complete) have been described, could further modulate VDR expression in ethnic-, disease- or tissue/cell-specific contexts (17,19,20).

A number of studies have suggested potential associations between these VDR variants and psoriasis. However, the results have been inconsistent, even within certain populations, possibly due to ethnic genetic or epigenetic variation and/or differences in psoriasis clinical spectrum among cohorts, emphasizing the need for ethnically and clinically stratified research. In addition, associations between these VDR SNPs and psoriasis-related clinical features remain understudied and may benefit from phenotype stratification (15,16,21-23).

To the best of our knowledge, the impact of VDR FokI, BsmI and TaqI on psoriasis has not yet been studied in the Greek population. Given the ethnic variability in genetic polymorphisms (18) and the clinical diversity of psoriasis across studies, this study aimed to investigate the role of three common VDR gene variants, namely FokI (rs2228570), BsmI (rs1544410) and TaqI (rs731236), in PsV susceptibility and clinical phenotype in a Caucasian Greek cohort (Fig. 2).

Patients and methods

Study design, population and settings. In this single-center, cross-sectional study, unrelated adult subjects of Caucasian Greek origin (203 PsV cases and 812 controls) were included. The cases were prospectively enrolled from January 2019 to December 2022 at the psoriasis outpatient unit of 'A. Sygros' Hospital (Athens, Greece) and met the following inclusion criteria: i) Age ≥18 years; ii) confirmed PsV diagnosis, with or without psoriatic arthritis (PsA); and iii) Greek ancestry. Patients aged <18 years, those with non-plaque psoriasis subtypes or non-Greek ancestry and affected first- to third-degree blood relatives of enrolled participants were excluded from the study. Controls comprised age (±5 years)-, sex- and ethnicity-matched unrelated individuals from the general population. The control group data were retrospectively obtained from fully anonymized and de-identified datasets provided by New Genomed LLC for research purposes, based on a collaboration framework between New Genomed LLC and the National and Kapodistrian University of Athens (Athens, Greece). The study protocol was approved by the Institutional Review Board of 'A. Sygros' Hospital (approval no. 2962/13-6-2018) and conducted in accordance with the Helsinki Declaration. All participants provided written informed consent for blood collection, genotyping and use of their genetic and demographic data for research purposes, following the European Medicines Agency guidelines (24).

Clinico-epidemiological assessments. PsV was diagnosed clinically and/or histologically by board-certified dermatologists. Predefined sociodemographic and disease-related clinical data were collected through standardized questionnaires. Disease severity was assessed based on previous international consensus criteria (25): Patients with a body surface area (BSA) <10 and/or no affected special location (scalp, face, palms/soles, nails or genitalia) who were managed exclusively with topical agents were classified as mild; cases with BSA ≥10 and/or special site involvement and/or a history of systemic treatment or phototherapy were categorized as severe. Early-onset PsV was defined as disease initiation before age 40 and familial psoriasis was recorded when one or more first- to third-degree relatives were affected. Data collected from control subjects included age, sex and ethnicity.

Sample collection, DNA extraction and genotyping. Peripheral blood (5 ml) was collected from PsV cases into EDTA tubes. Genomic DNA was isolated using the PureLink™ Genomic DNA Mini Kit (Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol and stored at -20˚C until

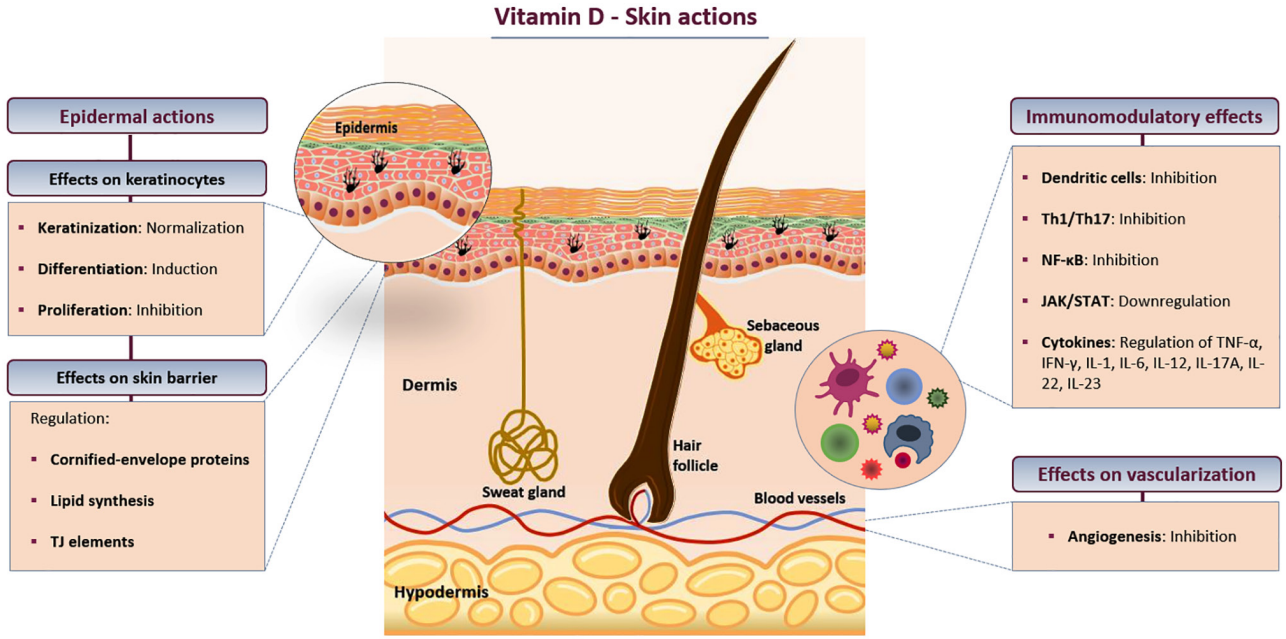

Figure 1. Summary of the main effects of vitamin D on skin barrier, immunity and vascularization. TJ, tight junctions; Th, T helper; JAK/STAT, Janus kinase/signal transducer and activator of transcription.

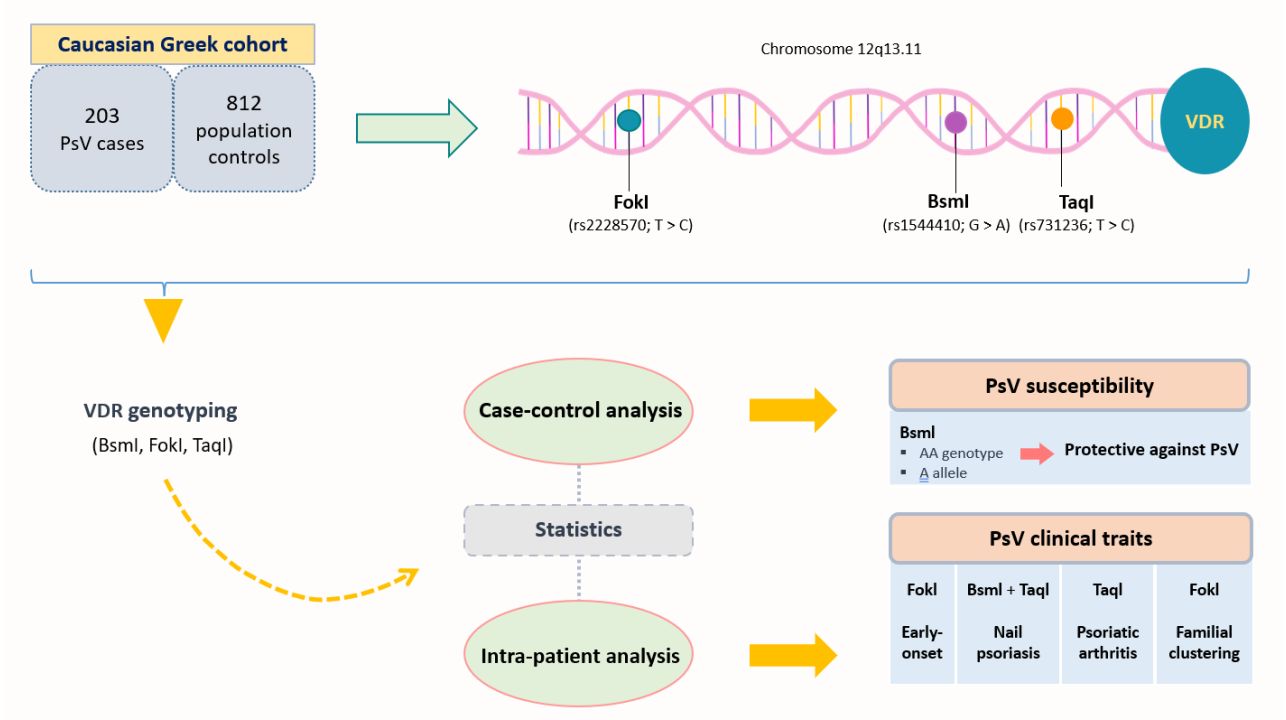

Figure 2. Graphical abstract summarizing the study design and main findings. BsmI was associated with PsV susceptibility, while VDR variants were associated with key clinical features, including age at onset (FokI), nail psoriasis (BsmI and TaqI), psoriatic arthritis (TaqI) and familial clustering (FokI). PsV, psoriasis vulgaris; VDR, vitamin D receptor.

analysis. Genotyping of the selected VDR SNPs, namely FokI (rs2228570), BsmI (rs1544410) and TaqI (rs731236), was carried out by real-time PCR on a LightCycler® 480 System (Roche Diagnostics GmbH) using allele-specific simple probes (LightSNiP assays; TIB MOLBIOL Syntheselabor GmbH), with all primers and probes supplied as part of the commercial assay and used according to the manufacturer's instructions, followed by melting-curve analysis. Genotype determination was based on the manufacturer-defined melting-peak profiles. Primer/probe sequence information is not disclosed by the manufacturer.

Statistical analysis. Descriptive statistics are presented as frequencies with percentages for categorical data and as

Table I. Epidemiological and disease-specific clinical data of the study population.

Clinico-epidemiological data	PsV cases (n=203)	Controls (n=812)	P-value[a]
Sex, n (%)			0.395
Male	129 (63.6)	487 (60.0)	
Female	74 (36.4)	325 (40.0)	
Median age, years (IQR; range)	54 (44.0-64.0; 22-86)	55 (45.0-65.0; 22-91)	0.310
Median BMI, kg/m^2 (IQR; range)	28.6 (24.6-32.5; 18.4-49.4)	-	-
Overweight/obese (BMI ≥25), n (%)	142 (70.0)	-	-
Normal weight (BMI, <25), n (%)	61 (30.0)	-	-
Smoking status, n (%)			
Current	98 (48.3)	-	-
Former	50 (24.6)	-	-
Never	55 (27.1)	-	-
Median age at PsV onset, years (IQR; range)	32 (20.0-44.0; 5-66)	-	-
Early-onset PsV (<40 years), n (%)	136 (67.0)	-	-
Median disease duration, years (IQR; range)	19 (10.0-30.0; 1-60)	-	-
Disease severity, n (%)			
Mild	47 (23.2)	-	-
Severe	156 (76.8)	-	-
Special site involvement, n (%)			
Nails	85 (41.9)	-	-
Scalp	115 (56.7)	-	-
Genitals	55 (27.1)	-	-
Koebner response (yes), n (%)	68 (33.5)	-	-
Psoriasis family history (yes), n (%)	112 (55.2)	-	-
Comorbidities (yes), n (%)	168 (82.8)	-	-
Metabolic disease[b]	96 (47.3)	-	-
PsA	62 (30.5)	-	-
Thyroid disorder	56 (27.6)	-	-
Current treatment (yes), n (%)	185 (91.1)	-	-
Topical	29 (15.7)	-	-
Phototherapy	4 (2.2)	-	-
Systemic	152 (82.1)	-	-

BMI was calculated as weight in kilograms divided by height in meters squared. [a]P-value for χ2 test (sex) and Mann-Whitney U (age) tests; [b]presence of hypertension or type 2 diabetes mellitus. IQR, interquartile range; PsA, psoriatic arthritis; PsV, psoriasis vulgaris.

means ± SD or medians with interquartile range (IQR) for continuous variables after assessment of normality by the Shapiro-Wilk test. Associations of VDR variants with PsV susceptibility (PsV cases vs. controls) and clinical variables (intra-patient comparisons) were evaluated using logistic regression or χ^2/Fisher's exact test, as appropriate, to calculate odds ratios (ORs) with 95% CIs. All association analyses were conducted under dominant, recessive, overdominant and allelic genetic models, with the major allele as the reference. The Benjamini-Hochberg false discovery rate (FDR) correction was applied to adjust P-values for multiple testing at a significance level of 5%. The Hardy-Weinberg equilibrium (HWE) for each SNP was assessed among controls using the χ^2 test, with P>0.05 indicating no significant deviation. All analyses were two-sided and performed using STATA/IC (version 16.1; StataCorp, LLC).

Results

Sociodemographic and clinical disease-specific data. A total of 1,015 unrelated Greek subjects [203 patients with PsV (63.6% male) and 812 controls (60% male); case-control ratio 1:4] were included in the study. The median age was 54 years (IQR: 44-64; range: 22-86) in the PsV group and 55 years (IQR: 45-65; range: 22-91) in the control group, with no significant difference in age (P=0.310) or sex distribution (P=0.395). Among PsV cases, the median age at PsV onset was 32 years (IQR: 20-44; range: 5-66) and 136 (67%) patients had early-onset disease (<40 years). Severe PsV was observed in 156 (76.8%) cases. Special site involvement included the scalp in 115 (56.7%), nails in 85 (41.9%) and genitals in 55 (27.1%) patients, while the Koebner phenomenon was present in 68 (33.5%). A family history of psoriasis was reported in

Table II. Genotype and allele frequency distribution of the VDR SNPs in PsV cases and controls.

A, FokI (rs2228570)

Genotype/allele	PsV cases (n=203), n (%)	Controls (n=812), n (%)
CC	96 (47.29)	380 (46.80)
TC	83 (40.89)	348 (42.86)
TT	24 (11.82)	84 (10.34)
C	275 (67.73)	1,108 (68.23)
T	131 (32.27)	516 (31.77)
HWE P-value	-	0.743

B, BsmI (rs1544410)

Genotype/allele	PsV cases (n=203), n (%)	Controls (n=812), n (%)
GG	62 (30.54)	214 (26.36)
GA	107 (52.71)	388 (47.78)
AA	34 (16.75)	210 (25.86)
G	231 (56.90)	816 (50.25)
A	175 (43.10)	808 (49.75)
HWE P-value	-	0.206

C, TaqI (rs731236)

Genotype/allele	PsV cases (n=203), n (%)	Controls (n=812), n (%)
TT	65 (32.02)	252 (31.03)
CT	88 (43.35)	390 (48.03)
CC	50 (24.63)	170 (20.94)
T	218 (53.69)	894 (55.05)
C	188 (46.31)	730 (44.95)
HWE P-value	-	0.400

P-values are from the χ^2 test for HWE. HWE, Hardy-Weinberg equilibrium; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

112 (55.2%) patients. Metabolic comorbidities and PsA were the most commonly associated conditions (47.3 and 30.5%, respectively). Sociodemographic and clinical disease-related data of the study group are summarized in Table I.

Genotype and allele distributions of VDR variants in PsV cases vs. controls. Genotype and allele frequency distributions of the studied VDR SNPs in PsV cases and controls and their associations with PsV susceptibility are presented in Tables II and III. Genotype frequencies of all VDR variants were in HWE among controls (FokI, P=0.743; BsmI, P=0.206; TaqI, P=0.400).

After FDR correction, the BsmI variant remained significantly associated with PsV susceptibility in both the recessive (AA vs. GA + GG; OR: 0.577; 95% CI: 0.386-0.861; P=0.007; adjusted P=0.028) and allelic (A vs. G; OR: 0.765; 95% CI: 0.614-0.953; P=0.016; adjusted P=0.032) models. The AA genotype and A allele of BsmI were less common in PsV cases compared with controls (16.8 vs. 25.9% and 43.1 vs. 49.8%, respectively), suggesting a protective effect against PsV. No significant differences were found between PsV cases and controls for the FokI and TaqI variants in any of the models studied, indicating no association with PsV susceptibility in this cohort.

Subgroup analysis based on disease-specific clinical features. Among PsV cases, intra-patient subgroup analyses revealed significant associations with disease-related clinical traits. In comparisons between early- and late-onset PsV cases (<40 vs. ≥40 years), the FokI variant was significantly associated with age at disease onset in both the dominant (TT + TC vs. CC; OR: 2.551; 95% CI: 1.396-4.660; P=0.002; adjusted P=0.036) and allelic (T vs. C; OR: 2.172; 95% CI: 1.346-3.507; P=0.001; adjusted P=0.022) models, suggesting that presence of the T allele may predispose to earlier onset of PsV (Tables IV and V). Regarding special-site involvement, both BsmI and TaqI exhibited significant associations with nail psoriasis, as shown in Tables VI and VII. BsmI was associated with psoriatic onychia in the dominant (AA + GA vs. GG; OR: 2.755; 95% CI: 1.427-5.319; P=0.003; adjusted P=0.040) and allelic (A vs. G; OR: 1.999; 95% CI: 1.337-2.986; P=0.001; adjusted P=0.022) models, indicating that presence of the A allele may increase the risk of nail involvement. Similarly, TaqI C allele presence was associated with nail disease under both the dominant (CC + CT vs. TT; OR: 3.063; 95% CI: 1.590-5.899; P=0.001; adjusted P=0.022) and allelic (C vs. T; OR: 1.948; 95% CI: 1.305-2.907; P=0.001; adjusted P=0.022) models.

In comparisons based on comorbid PsA, the TaqI variant exhibited a significant association under the allelic model (C vs. T; OR: 0.477; 95% CI: 0.308-0.741; P=0.001; adjusted P=0.022), suggesting that carriers of the C allele (CC/CT) may be less likely to develop PsA (Table VIII and IX).

In analyses stratified by family history of psoriasis, the recessive model of FokI (TT vs. TC + CC; OR: 6.769; 95% CI: 1.950-23.503; P=0.003; adjusted P=0.040) was significantly associated with familial disease, indicating that the TT genotype may contribute to familial clustering of psoriasis (Tables X and XI).

The studied VDR SNPs showed no evidence of association with other clinico-epidemiological parameters, including BMI, disease severity, scalp or genital involvement and the Koebner phenomenon, in this cohort (all P>0.05; Tables SI-SVIII). A graphical abstract summarizing the study design and main findings is provided in Fig. 2.

Discussion

In this study, the role of three common VDR variants (FokI, BsmI and TaqI) in PsV susceptibility and clinical phenotype was evaluated in a Caucasian Greek cohort. The case-control analysis supported an association between BsmI and PsV susceptibility in the recessive and allelic models, whereas no associations were observed for FokI or TaqI. Subgroup

Table III. Genetic model analysis of the VDR SNPs in PsV cases and controls.

A, FokI (rs2228570)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant TT + TC vs. CC	0.980 (0.720-1.334)	0.900	0.900
Recessive TT vs. TC + CC	1.162 (0.717-1.882)	0.542	0.900
Overdominant TC vs. TT + CC	0.922 (0.675-1.260)	0.611	0.900
Allelic T vs. C	1.023 (0.810-1.291)	0.849	0.900

B, BsmI (rs1544410)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant AA + GA vs. GG	0.814 (0.581-1.140)	0.231	0.231
Recessive AA vs. GA + GG	0.577 (0.386-0.861)	0.007	0.028
Overdominant GA vs. GG + AA	1.218 (0.895-1.657)	0.210	0.231
Allelic A vs. G	0.765 (0.614-0.953)	0.016	0.032

C, TaqI (rs731236)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant CC + CT vs. TT	0.955 (0.687-1.329)	0.786	0.786
Recessive CC vs. CT + TT	1.234 (0.860-1.771)	0.254	0.508
Overdominant CT vs. TT + CC	0.828 (0.607-1.129)	0.233	0.508
Allelic C vs. T	1.056 (0.849-1.314)	0.624	0.786

P-values were adjusted by Benjamini-Hochberg correction. OR, odds ratio; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

Table IV. Genotype and allele frequency distribution of the VDR SNPs in early- and late-onset PsV cases.

A, FokI (rs2228570)

Genotype/allele	Early PsV <40 years (n=136), n (%)	Late PsV ≥40 years (n=67), n (%)
CC	54 (39.71)	42 (62.69)
TC	62 (45.59)	21 (31.34)
TT	20 (14.70)	4 (5.97)
C	170 (62.50)	105 (78.36)
T	102 (37.50)	29 (21.64)

B, BsmI (rs1544410)

Genotype/allele	Early PsV <40 years (n=136), n (%)	Late PsV ≥40 years (n=67), n (%)
GG	43 (31.62)	19 (28.36)
GA	74 (54.41)	33 (49.25)
AA	19 (13.97)	15 (22.39)
G	160 (58.82)	71 (52.99)
A	112 (41.18)	63 (47.01)

Table IV. Continued.

C, TaqI (rs731236)

Genotype/allele	Early PsV <40 years (n=136), n (%)	Late PsV ≥40 years (n=67), n (%)
TT	46 (33.82)	19 (28.36)
CT	60 (44.12)	28 (41.79)
CC	30 (22.06)	20 (29.85)
T	152 (55.88)	66 (49.25)
C	120 (44.12)	68 (50.75)

PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

comparisons further indicated associations with major disease-related clinical traits, including age at onset, nail or joint involvement and familial clustering.

For BsmI, carriers of the AA genotype exhibited a 42.3% reduced risk of PsV compared with G-allele carriers (GA/GG). The allelic model further supported this pattern, demonstrating a protective effect of the A allele against PsV. The

Table V. Genetic model analysis of the VDR SNPs in early- and late-onset PsV cases.

A, FokI (rs2228570)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant TT + TC vs. CC	2.551 (1.396-4.660)	0.002	0.036
Recessive TT vs. TC + CC	2.716 (0.889-8.293)	0.079	0.404
Overdominant TC vs. TT + CC	1.835 (0.991-3.400)	0.054	0.364
Allelic T vs. C	2.172 (1.346-3.507)	0.001	0.022

B, BsmI (rs1544410)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant AA + GA vs. GG	0.856 (0.450-1.628)	0.636	0.830
Recessive AA vs. GA + GG	0.563 (0.265-1.194)	0.134	0.499
Overdominant GA vs. GG + AA	1.230 (0.684-2.209)	0.489	0.734
Allelic A vs. G	0.789 (0.509-1.223)	0.264	0.641

C, TaqI (rs731236)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant CC + CT vs. TT	0.774 (0.409-1.467)	0.433	0.718
Recessive CC vs. CT + TT	0.665 (0.343-1.289)	0.227	0.641
Overdominant CT vs. TT + CC	1.100 (0.608-1.987)	0.753	0.894
Allelic C vs. T	0.766 (0.495-1.185)	0.208	0.641

P-values were adjusted by Benjamini-Hochberg correction. OR, odds ratio; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

Table VI. Genotype and allele frequency distribution of the VDR SNPs in PsV cases with and without nail involvement.

A, FokI (rs2228570)

Genotype/allele	With nail PsV (n=85), n (%)	Without nail PsV (n=118), n (%)
CC	36 (42.35)	60 (50.85)
TC	38 (44.71)	45 (38.14)
TT	11 (12.94)	13 (11.01)
C	110 (64.71)	165 (69.92)
T	60 (35.29)	71 (30.08)

B, BsmI (rs1544410)

Genotype/allele	With nail PsV (n=85), n (%)	Without nail PsV (n=118), n (%)
GG	16 (18.82)	46 (38.98)
GA	48 (56.47)	59 (50.00)
AA	21 (24.71)	13 (11.02)
G	80 (47.06)	151 (63.98)
A	90 (52.94)	85 (36.02)

Table VI. Continued.

C, TaqI (rs731236)

Genotype/allele	With nail PsV (n=85), n (%)	Without nail PsV (n=118), n (%)
TT	16 (18.82)	49 (41.52)
CT	43 (50.59)	45 (38.14)
CC	26 (30.59)	24 (20.34)
T	75 (44.12)	143 (60.59)
C	95 (55.88)	93 (39.41)

PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

BsmI variant has already been associated with psoriasis, but findings vary by ethnicity (21,23,26,27). The present results align with case-control studies and meta-analyses indicating a protective role of the A allele and/or AA genotype in Caucasian and Asian populations (21,23,27). In this context, a Japanese study reported increased PsV risk for the GG genotype, while the A allele and AA genotype appeared protective (27). Two

Table VII. Genetic model analysis of the VDR SNPs in PsV cases with and without nail involvement.

A, FokI (rs2228570)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant TT + TC vs. CC	1.408 (0.803-2.469)	0.232	0.641
Recessive TT vs. TC + CC	1.200 (0.510-2.824)	0.676	0.859
Overdominant TC vs. TT + CC	1.312 (0.744-2.311)	0.348	0.659
Allelic T vs. C	1.268 (0.833-1.929)	0.268	0.641

B, BsmI (rs1544410)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant AA + GA vs. GG	2.755 (1.427-5.319)	0.003	0.040
Recessive AA vs. GA + GG	2.650 (1.242-5.657)	0.012	0.108
Overdominant GA vs. GG + AA	1.297 (0.741-2.272)	0.363	0.676
Allelic A vs. G	1.999 (1.337-2.986)	0.001	0.022

C, TaqI (rs731236)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant CC + CT vs. TT	3.063 (1.590-5.899)	0.001	0.022
Recessive CC vs. CT + TT	1.725 (0.907-3.280)	0.096	0.432
Overdominant CT vs. TT + CC	1.661 (0.944-2.921)	0.078	0.404
Allelic C vs. T	1.948 (1.305-2.907)	0.001	0.022

P-values were adjusted by Benjamini-Hochberg correction. OR, odds ratio; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

Table VIII. Genotype and allele frequency distribution of the VDR SNPs in PsV cases with and without psoriatic arthritis.

A, FokI (rs2228570)

Genotype/allele	With PsA (n=62), n (%)	Without PsA (n=141), n (%)
CC	30 (48.39)	66 (46.81)
TC	27 (43.55)	56 (39.72)
TT	5 (8.06)	19 (13.47)
C	87 (70.16)	188 (66.67)
T	37 (29.84)	94 (33.33)

B, BsmI (rs1544410)

Genotype/allele	With PsA (n=62), n (%)	Without PsA (n=141), n (%)
GG	25 (40.32)	37 (26.24)
GA	27 (43.55)	80 (56.74)
AA	10 (16.13)	24 (17.02)
G	77 (62.10)	154 (54.61)
A	47 (37.90)	128 (45.39)

Table VIII. Continued.

C, TaqI (rs731236)

Genotype/allele	With PsA (n=62), n (%)	Without PsA (n=141), n (%)
TT	28 (45.16)	37 (26.24)
CT	26 (41.94)	62 (43.97)
CC	8 (12.90)	42 (29.79)
T	82 (66.13)	136 (48.23)
C	42 (33.87)	146 (51.77)

PsA, psoriatic arthritis; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

meta-analyses supported this trend, demonstrating an inverse association between the A allele and PsV risk in overall populations, although significance was lost after correction and in Asian populations, despite undefined psoriasis subtypes and precluded intra-European evaluation (21,23). However, additional studies have found no association or even opposite effects (15,22,28).

Table IX. Genetic model analysis of the VDR SNPs in PsV cases with and without psoriatic arthritis.

A, FokI (rs2228570)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant TT + TC vs. CC	0.939 (0.516-1.707)	0.836	0.921
Recessive TT vs. TC + CC	0.563 (0.200-1.586)	0.277	0.641
Overdominant TC vs. TT + CC	1.171 (0.640-2.146)	0.609	0.822
Allelic T vs. C	0.851 (0.538-1.344)	0.488	0.734

B, BsmI (rs1544410)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant AA + GA vs. GG	0.527 (0.280-0.990)	0.046	0.355
Recessive AA vs. GA + GG	0.938 (0.418-2.101)	0.875	0.921
Overdominant GA vs. GG + AA	0.588 (0.322-1.074)	0.084	0.404
Allelic A vs. G	0.734 (0.465-1.155)	0.161	0.561

C, TaqI (rs731236)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant CC + CT vs. TT	0.432 (0.231-0.807)	0.009	0.108
Recessive CC vs. CT + TT	0.349 (0.153-0.797)	0.012	0.108
Overdominant CT vs. TT + CC	0.920 (0.503-1.683)	0.787	0.914
Allelic C vs. T	0.477 (0.308-0.741)	0.001	0.022

P-values were adjusted by Benjamini-Hochberg correction. OR, odds ratio; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

In this context, the present data suggest that among the studied VDR variants, BsmI may represent a PsV susceptibility-related marker in the Greek population. From a biological perspective, this 3' non-coding variant may be associated with regulation of VDR expression (i.e., via altered mRNA stability and/or LD with functional polymorphisms), rather than receptor structural changes (16-19). Altered VDR expression may, in turn, affect VitD/VDR-mediated signaling relevant to PsV pathogenesis, given the roles of VitD in key processes involved in psoriatic inflammation, including keratinocyte proliferation/differentiation, epidermal barrier function and immune responses (5-9). However, further research is needed to determine whether rs1544410 itself has regulatory effects or reflects other functional variants, particularly given population and/or ethnic differences in LD architecture (18).

Both FokI and TaqI showed no impact on PsV susceptibility in the present cohort. Although findings vary among populations (15,21-23,28), a number of studies in Caucasian, Asian and North African (Egyptian) groups have similarly reported no association between these variants and PsV risk (21,29-34). Divergent results across studies may reflect differences in ethnic or population genetic backgrounds, including LD structure, as well as in epigenetic variation, environmental exposures or methodological factors such as study design, sample size or psoriasis subtype composition (18).

Intra-patient analyses indicated additional phenotype-specific associations. Among PsV cases, FokI appeared to be associated with age at disease onset under the dominant and allelic models. In the dominant model (TT + TC vs. CC), T-allele carriers (TT/TC) exhibited a nearly 2.6-fold increased risk of early-onset PsV (<40 years). This was further supported by the allelic model (T vs. C), indicating that the FokI T allele may predispose to earlier disease onset. Although age-at-onset effects of VDR SNPs have been explored (33-42), only one study has shown an association between the BsmI GG genotype and early-onset disease (<40 years) in a Caucasian (Turkish) cohort of mixed psoriasis subtypes (n=102) (37).

FokI was also associated with familial psoriasis under the recessive model (TT vs. TC + CC). Patients with PsV carrying the TT genotype were nearly 6.8 times more likely to report an affected first- to third-degree relative compared with C-allele carriers (TC/CC), suggesting that FokI may play a role in heritable patterns of psoriasis. Although not directly comparable, a study in a Caucasian (British) PsV cohort (n=205) found that the FokI C allele combined with a promoter variant reduced the risk of non-familial (sporadic) psoriasis (34). Since that effect was haplotype-dependent, the present finding may represent one of the first single-variant indications that FokI itself could contribute to familial clustering of psoriasis.

Table X. Genotype and allele frequency distribution of the VDR SNPs in PsV cases with and without psoriasis family history.

A, FokI (rs2228570)

Genotype/allele	With psoriasis FH (n=112), n (%)	Without psoriasis FH (n=91), n (%)
CC	49 (43.75)	47 (51.65)
TC	42 (37.50)	41 (45.05)
TT	21 (18.75)	3 (3.30)
C	140 (62.50)	135 (74.18)
T	84 (37.50)	47 (25.82)

B, BsmI (rs1544410)

Genotype/allele	With psoriasis FH (n=112), n (%)	Without psoriasis FH (n=91), n (%)
GG	38 (33.92)	24 (26.37)
GA	58 (51.79)	49 (53.85)
AA	16 (14.29)	18 (19.78)
G	134 (59.82)	97 (53.30)
A	90 (40.18)	85 (46.70)

C, TaqI (rs731236)

Genotype/allele	With psoriasis FH (n=112), n (%)	Without psoriasis FH (n=91), n (%)
TT	40 (35.71)	25 (27.48)
CT	45 (40.18)	43 (47.25)
CC	27 (24.11)	23 (25.27)
T	125 (55.80)	93 (51.10)
C	99 (44.20)	89 (48.90)

FH, family history; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

Notably, the FokI TT genotype in this cohort seemed to be associated with both early-onset PsV and familial disease, features that frequently co-occur clinically, as early-onset psoriasis tends to cluster in families (43). Mechanistically, FokI (T-to-C substitution) alters the translation initiation site (ATG to ACG), resulting in a longer, less active VDR isoform in T allele carriers (16-19), which may impair downstream VitD/VDR-mediated effects on skin homeostasis and immune responses. Thus, compromised VitD/VDR signaling in TT homozygotes may reflect a genetic overlap, potentially involving FokI, which could contribute to both familial aggregation and early disease onset. This aligns with the known clinical tendency of early-onset PsV to cluster in families (43), but requires further validation.

Significant associations were also observed for nail psoriasis with both BsmI and TaqI under the dominant and allelic models. In the dominant model, carriers of the BsmI A allele (AA/GA) and the TaqI C allele (CC/CT) exhibited a ~2.8- and ~3.1-fold increased risk of nail involvement, respectively. The allelic models also indicated higher risk of nail disease for both the BsmI A and TaqI C alleles. This contrasts with an Asian (Korean) PsV cohort (n=104) in which neither variant was associated with nail psoriasis (40).

TaqI was further associated with PsA comorbidity under the allelic model (C vs. T), indicating that the C allele may protect against joint disease in this cohort. Although relevant data are limited (40,44,45), a Caucasian (Turkish) study (n=51) has similarly shown an association between the TaqI T allele and increased PsA risk (44). These findings suggest that TaqI may influence extra-cutaneous manifestations of PsV, modulating the overall disease burden beyond the skin.

Of note, while the BsmI A allele seemed to be protective in the present case-control setting, it was associated with nail involvement among PsV cases. This pattern may indicate phenotype-modifying effects after disease onset. Although the functional impact of VDR variants on VitD signaling remains unclear, both BsmI and TaqI may exert tissue- and/or cell-specific regulatory effects on VDR expression (18,19), potentially influencing phenotype-specific inflammatory cascades involved in nail psoriasis. In addition, as the TaqI C allele creates a CpG site prone to DNA methylation (17,19,20), the present findings suggest that, in addition to genetic variation, epigenetic modifications at this locus may underlie tissue-specific inflammation, with possible implications for both nail and joint disease.

Furthermore, the TaqI C allele in this cohort was associated with both psoriatic onychia and arthritis, two clinically related features, but with inverse effect patterns. While nail involvement often predicts increased arthritis risk (1,46), the C allele appeared to be protective against PsA while predisposing to nail disease. These divergent effects within the nail-joint axis may arise from distinct genetic and/or epigenetic drivers, including differences in the genetic architecture of cutaneous vs. joint disease (1,47) and in allele-dependent TaqI methylation (17,19,20), potentially resulting in tissue-specific VitD/VDR signaling. As methylation status varies by ethnicity, disease state or tissue type (17,19,48), TaqI may exert phenotype-specific effects driven by context-dependent epigenetic regulation. This warrants further investigation within the nail-joint spectrum of psoriatic disease.

Key strengths of the present study include the focus on a single ethnic group (Greek subjects) and a specific psoriasis subtype (PsV), reducing genetic and phenotypic heterogeneity. The relatively large control group (n=812; 1:4 case-control ratio) is also an advantage compared with commonly used 1:1 or 1:2 designs in genetic association studies (15,22,23,28). In addition, the inclusion of several clinical traits, beyond case-control comparisons, provides insights into whether VDR variation may contribute to PsV phenotype. The FDR correction for multiple testing further improves the reliability of the results.

However, certain limitations require consideration. First, the PsV sample (n=203) is relatively modest for detecting subtle effects. Second, although the single-center, ethnically and clinically uniform design enhances internal validity, it may limit the generalizability of the present findings to other

Table XI. Genetic model analysis of the VDR SNPs in PsV cases with and without psoriasis family history.

A, FokI (rs2228570)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant TT + TC vs. CC	1.373 (0.788-2.393)	0.263	0.641
Recessive TT vs. TC + CC	6.769 (1.950-23.503)	0.003	0.040
Overdominant TC vs. TT + CC	0.731 (0.417-1.285)	0.277	0.641
Allelic T vs. C	1.723 (1.123-2.645)	0.012	0.108

B, BsmI (rs1544410)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant AA + GA vs. GG	0.698 (0.380-1.282)	0.246	0.641
Recessive AA vs. GA + GG	0.676 (0.323-1.415)	0.299	0.659
Overdominant GA vs. GG + AA	0.921 (0.529-1.603)	0.770	0.904
Allelic A vs. G	0.766 (0.506-1.160)	0.187	0.631

C, TaqI (rs731236)

Genetic model	OR (95% CI)	P-value	Adjusted P-value
Dominant CC + CT vs. TT	0.682 (0.374-1.244)	0.212	0.641
Recessive CC vs. CT + TT	0.939 (0.495-1.783)	0.848	0.921
Overdominant CT vs. TT + CC	0.750 (0.429-1.311)	0.312	0.659
Allelic C vs. T	0.828 (0.548-1.249)	0.344	0.659

P-values were adjusted by Benjamini-Hochberg correction. OR, odds ratio; PsV, psoriasis vulgaris; SNPs, single nucleotide polymorphisms; VDR, vitamin D receptor.

psoriasis subtypes or populations with different genetic, epigenetic or environmental backgrounds. In addition, while cases and controls were matched on age, sex and ethnicity, the population controls lacked detailed clinical and exposure data, preventing detection of psoriasis status or potential confounders. However, given the national psoriasis prevalence in Greece (~2.2%) (2,49), the expected number of psoriasis cases among 812 controls is low, reducing, but not eliminating, the risk of misclassification. Furthermore, only three VDR SNPs were analyzed, without investigating rare variants or haplotypes. Finally, VitD-related confounders (VitD serum levels, dietary or supplemental intake, sun exposure), which could influence VDR activity, were not assessed.

While VDR has not emerged as a psoriasis susceptibility locus in genome-wide association studies (GWAS) (3), several lines of evidence still support its biological relevance, including the role of the VitD/VDR axis in key psoriatic components, altered VDR expression in psoriatic skin, the widespread use of topical VitD analogs in psoriasis treatment, variable but suggestive associations for FokI, BsmI and TaqI in prior studies and the potential epigenetic regulation at the TaqI CpG site (5-9,15-17,19-23). Emerging data also indicate additional cutaneous VitD-related bioactive metabolites, some with alternative receptor targets, underscoring the broader secosteroid network in the skin (10). By design, GWAS, which apply stringent significance thresholds and often treat psoriasis as a single trait across diverse clinical and ethnic backgrounds, could miss variants with small-to-moderate or indirect effects influenced by LD patterns and/or ethnic-, disease subtype- or epigenetic-related factors (19,50,51). Thus, the associations observed in the present genetically and clinically uniform cohort could reflect ethnic- and/or phenotype-specific VDR effects that may be too weak to be captured in GWAS (19).

In conclusion, to the best of our knowledge, this was the first study to explore VDR FokI (rs2228570), BsmI (rs1544410) and TaqI (rs731236) variants in association with PsV in a Greek population. The present results showed that BsmI may contribute to disease susceptibility, while all three polymorphisms may influence major clinical traits, including age at onset, nail or joint involvement and familial clustering of PsV.

Although the functional consequences of these variants are not fully elucidated, VDR genetic variation and epigenetic modification may alter receptor activity or expression levels, potentially modulating key processes disrupted in psoriasis. In this regard, the present findings suggest that common VDR variants may exert small, context-dependent effects that could play a role in PsV initiation and phenotypic expression. Thus, the VDR locus may represent a potential biomarker for personalized risk stratification and clinical profiling in PsV. Further prospective studies in larger Caucasian cohorts, integrating

both genotypic and phenotypic data, are needed to validate these findings and further elucidate the complex genetic basis of PsV, particularly its links to VitD/VDR signaling and its potential clinical implications.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ND and EN conceived and designed the study. PS and NR contributed to clinical and laboratory data collection. MK designed the experiments and AT, MP and PS performed the laboratory analyses. AF supervised the statistical analyses and contributed to statistical interpretation. PS conducted the literature review, prepared the figures and tables and wrote the initial draft of the manuscript. PS, MK, MP, NR, IS, AJS and DAS contributed to data interpretation and critically revised the manuscript. PS finalized the manuscript under the supervision of ND and EN. PS, MK and ND confirm the authenticity of all the raw data. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the ethical standards of the Institutional Review Board of 'A. Sygros' Hospital (approval no. 2962/13-6-2018) and the Helsinki Declaration. Written informed consent was obtained from all participants prior to enrollment.

Patient consent for publication

Written informed consent for publication of anonymized, de-identified clinical and genetic data was obtained from all participants.

Competing interests

DAS is the Editor-in-Chief of the journal but had no personal involvement in the reviewing process or any influence in terms of adjudicating on the final decision, for the present article. The other authors declare that they have no competing interests.

References

1. Griffiths CEM, Armstrong AW, Gudjonsson JE and Barker JNWN: Psoriasis. Lancet 397: 1301-1315, 2021.
2. Damiani G, Bragazzi NL, Karimkhani Aksut C, Wu D, Alicandro G, McGonagle D, Guo C, Dellavalle R, Grada A, Wong P, *et al*: The global, regional, and national burden of psoriasis: Results and insights from the global burden of disease 2019 study. Front Med (Lausanne) 8: 743180, 2021.
3. Zhang M, Su W, Deng J, Zhai B, Zhu G, Gao R, Zeng Q, Qiu J, Bian Z, Xiao H, *et al*: Multi-ancestry genome-wide meta-analysis with 472,819 individuals identifies 32 novel risk loci for psoriasis. J Transl Med 23: 133, 2025.
4. Singh S, Pradhan D, Puri P, Ramesh V, Aggarwal S, Nayek A and Jain AK: Genomic alterations driving psoriasis pathogenesis. Gene 683: 61-71, 2019.
5. Brożyna AA, Slominski RM, Nedoszytko B, Zmijewski MA and Slominski AT: Vitamin D signaling in psoriasis: Pathogenesis and therapy. Int J Mol Sci 23: 8575, 2022.
6. Gisondi P, Gracia-Cazaña T, Kurzen H and Galván J: Calcipotriol/Betamethasone dipropionate for the treatment of psoriasis: Mechanism of action and evidence of efficacy and safety versus topical corticosteroids. J Clin Med 13: 4484, 2024.
7. Visconti B, Paolino G, Carotti S, Pendolino AL, Morini S, Richetta AG and Calvieri S: Immunohistochemical expression of VDR is associated with reduced integrity of tight junction complex in psoriatic skin. J Eur Acad Dermatol Venereol 29: 2038-2042, 2015.
8. Liang W, Lin Z, Zhang L, Qin X, Zhang Y and Sun L: Calcipotriol inhibits proliferation of human keratinocytes by downregulating STAT1 and STAT3 signaling. J Investig Med 65: 376-381, 2017.
9. Cao M, Mei L, Xiao M, Li J and Fang F: Calcipotriol inhibits psoriasis-like angiogenic features in K14-VEGF transgenic mice. Eur J Dermatol 32: 24-33, 2022.
10. Slominski AT, Kim TK, Janjetovic Z, Slominski RM, Li W, Jetten AM, Indra AK, Mason RS and Tuckey RC: Biological Effects of CYP11A1-Derived Vitamin D and Lumisterol Metabolites in the Skin. J Invest Dermatol 144: 2145-2161, 2024.
11. Zhang Y, Jing D, Zhou G, Xiao Y, Shen M, Chen X and Liu H: Evidence of a causal relationship between vitamin D status and risk of psoriasis from the UK Biobank study. Front Nutr 9: 807344, 2022.
12. Lee YH and Song GG: Association between circulating 25-hydroxyvitamin D levels and psoriasis, and correlation with disease severity: A meta-analysis. Clin Exp Dermatol 43: 529-535, 2018.
13. Elmelid A, Siekkeri Vandikas M, Gillstedt M, Osmancevic A and Alsterholm M: The effect of narrow-band ultraviolet B phototherapy on free and total vitamin D serum levels in mild to severe plaque psoriasis. Biomolecules 13: 1018, 2023.
14. Elgarhy LH, Eltatawy RA, Rizk O and Ismail M: Vitamin D receptor expression in chronic plaque psoriasis before and after narrowband ultraviolet B phototherapy. J Cutan Aesthet Surg 16: 128-133, 2023.
15. Lee YH: Vitamin D receptor ApaI, TaqI, BsmI, and FokI polymorphisms and psoriasis susceptibility: An updated meta-analysis. Clin Exp Dermatol 44: 498-505, 2019.
16. Agliardi C, Guerini FR, Bolognesi E, Zanzottera M and Clerici M: VDR gene single nucleotide polymorphisms and autoimmunity: A narrative review. Biology (Basel) 12: 916, 2023.
17. Poon AH, Gong L, Brasch-Andersen C, Litonjua AA, Raby BA, Hamid Q, Laprise C, Weiss ST, Altman RB and Klein TE: Very important pharmacogene summary for VDR. Pharmacogenet Genomics 22: 758-763, 2012.
18. Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA and Van Leeuwen JP: Genetics and biology of vitamin D receptor polymorphisms. Gene 338: 143-156, 2004.
19. Saccone D, Asani F and Bornman L: Regulation of the vitamin D receptor gene by environment, genetics and epigenetics. Gene 561: 171-180, 2015.
20. Andraos C, Koorsen G, Knight JC and Bornman L: Vitamin D receptor gene methylation is associated with ethnicity, tuberculosis, and TaqI polymorphism. Hum Immunol 72: 262-268, 2011.
21. Stefanic M, Rucevic I and Barisic-Drusko V: Meta-analysis of vitamin D receptor polymorphisms and psoriasis risk. Int J Dermatol 52: 705-710, 2013.
22. Liu JL, Zhang SQ and Zeng HM: ApaI, BsmI, FokI and TaqI polymorphisms in the vitamin D receptor (VDR) gene and the risk of psoriasis: A meta-analysis. J Eur Acad Dermatol Venereol 27: 739-746, 2013.
23. Lee YH, Choi SJ, Ji JD and Song GG: Vitamin D receptor ApaI, TaqI, BsmI, and FokI polymorphisms and psoriasis susceptibility: A meta-analysis. Mol Biol Rep 39: 6471-6478, 2012.
24. European Medicines Agency: Position paper on terminology in pharmacogenetics. EMEA/CPMP/3070/01. EMEA, London, 2002. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/position-paper-terminology-pharmacogenetics_en.pdf.

25. Strober B, Ryan C, van de Kerkhof P, van der Walt J, Kimball AB, Barker J and Blauvelt A; International Psoriasis Council Board Members and Councilors: Recategorization of psoriasis severity: Delphi consensus from the International Psoriasis Council. J Am Acad Dermatol 82: 117-122, 2020.
26. AbdElneam AI, Al-Dhubaibi MS, Bahaj SS and Mohammed GF: The vitamin D receptor gene polymorphism rs1544410 T/T genotype as a predictor of factor vitamin D thresholds deficiency in patients with psoriasis vulgaris-A preliminary study. J Cosmet Dermatol 22: 1642-1646, 2023.
27. Saeki H, Asano N, Tsunemi Y, Takekoshi T, Kishimoto M, Mitsui H, Tada Y, Torii H, Komine M, Asahina A and Tamaki K: Polymorphisms of vitamin D receptor gene in Japanese patients with psoriasis vulgaris. J Dermatol Sci 30: 167-171, 2002.
28. Li J, Sun L, Sun J and Yan M: Pooling analysis regarding the impact of human vitamin D receptor variants on the odds of psoriasis. BMC Med Genet 20: 161, 2019.
29. A Anani HA, Khalifa WA, Althoqapy AA, Maklad SS, Kamal H, Sabry D and Samir M: Frequency of genotypes and allelic polymorphisms of vitamin D receptor in egyptian psoriatic patients and their association with disease severity, immune modulation of IL-22 levels and the response to topical calcipotriol treatment: A case control study. Indian J Dermatol 67: 37-44, 2022.
30. Liu J, Wang W, Liu K, Wan D, Wu Z, Cao Z, Luo Y, Xiao C and Yin M: Vitamin D receptor gene polymorphisms are associated with psoriasis susceptibility and the clinical response to calcipotriol in psoriatic patients. Exp Dermatol 29: 1186-1190, 2020.
31. Rucevic I, Stefanic M, Tokic S, Vuksic M, Glavas-Obrovac L and Barisic-Drusko V: Lack of association of vitamin D receptor gene 3'-haplotypes with psoriasis in Croatian patients. J Dermatol 39: 58-62, 2012.
32. Polić MV, Rucević I, Barisić-Drusko V, Miskulin M, Glavas-Obrovac L, Stefanić M, Karner I, Lipozencić J, Bacun T and Mihaljević I: Polymorphisms of vitamin D receptor gene in the population of eastern Croatia with psoriasis vulgaris and diabetes mellitus. Coll Antropol 36: 451-457, 2012.
33. Zuel-Fakkar NM, Kamel MM, Asaad MK, Mahran MZ and Shehab AA: A study of ApaI and TaqI genotypes of the vitamin D receptor in Egyptian patients with psoriasis. Clin Exp Dermatol 36: 355-359, 2011.
34. Halsall JA, Osborne JE, Pringle JH and Hutchinson PE: Vitamin D receptor gene polymorphisms, particularly the novel A-1012G promoter polymorphism, are associated with vitamin D3 responsiveness and non-familial susceptibility in psoriasis. Pharmacogenet Genomics 15:349-355, 2005.
35. Richetta AG, Silvestri V, Giancristoforo S, Rizzolo P, D'Epiro S, Graziano V, Mattozzi C, Navazio AS, Campoli M, D'Amico C, *et al*: A-1012G promoter polymorphism of vitamin D receptor gene is associated with psoriasis risk and lower allele-specific expression. DNA Cell Biol 33: 102-109, 2014.
36. Zhou X, Xu LD and Li YZ: The association of polymorphisms of the vitamin D receptor gene with psoriasis in the Han population of northeastern China. J Dermatol Sci 73: 63-66, 2014.
37. Acikbas I, Sanlı B, Tepeli E, Ergin S, Aktan S and Bagci H: Vitamin D receptor gene polymorphisms and haplotypes (Apa I, Bsm I, Fok I, Taq I) in Turkish psoriasis patients. Med Sci Monit 18: CR661-6, 2012.
38. Ruggiero M, Gulisano M, Peruzzi B, Giomi B, Caproni M, Fabbri P and Pacini S: Vitamin D receptor gene polymorphism is not associated with psoriasis in the Italian Caucasian population. J Dermatol Sci 35: 68-70, 2004.
39. Okita H, Ohtsuka T, Yamakage A and Yamazaki S: Polymorphism of the vitamin D(3) receptor in patients with psoriasis. Arch Dermatol Res 294: 159-162, 2002.
40. Park BS, Park JS, Lee DY, Youn JI and Kim IG: Vitamin D receptor polymorphism is associated with psoriasis. J Invest Dermatol 112: 113-116, 1999.
41. Mee JB and Cork MJ: Vitamin D receptor polymorphism and calcipotriol response in patients with psoriasis. J Invest Dermatol 110: 301-302, 1998.
42. Kontula K, Välimäki S, Kainulainen K, Viitanen AM and Keski-Oja J: Vitamin D receptor polymorphism and treatment of psoriasis with calcipotriol. Br J Dermatol 136: 977-978, 1997.
43. Ohata C, Anezaki H, Kaneko S, Okazaki F, Ito K, Matsuzaka Y, Kikuchi S, Koike Y, Murota H, Miyagi T, *et al*: Clinical characteristics of patients with psoriasis with family history: A multicenter observational study. J Dermatol 50: 746-752, 2023.
44. Dayangac-Erden D, Karaduman A and Erdem-Yurter H: Polymorphisms of vitamin D receptor gene in Turkish familial psoriasis patients. Arch Dermatol Res 299: 487-491, 2007.
45. Neves JSF, Visentainer JEL, Reis DMDS, Rocha Loures MA, Alves HV, Lara-Armi FF, de Alencar JB, Valentin Zacarias JM and Sell AM: The Influence of Vitamin D Receptor Gene Polymorphisms in Spondyloarthritis. Int J Inflam 2020: 8880879, 2020.
46. Langenbruch A, Radtke MA, Krensel M, Jacobi A, Reich K and Augustin M: Nail involvement as a predictor of concomitant psoriatic arthritis in patients with psoriasis. Br J Dermatol 171: 1123-1128, 2014.
47. Stuart PE, Nair RP, Tsoi LC, Tejasvi T, Das S, Kang HM, Ellinghaus E, Chandran V, Callis-Duffin K, Ike R, *et al*: Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. Am J Hum Genet 97: 816-836, 2015.
48. Meyer V, Saccone DS, Tugizimana F, Asani FF, Jeffery TJ and Bornman L: Methylation of the vitamin D receptor (VDR) Gene, together with genetic variation, race, and environment influence the signaling efficacy of the toll-like receptor 2/1-VDR pathway. Front Immunol 8: 1048, 2017.
49. Stratigos AJ, Richard MA, Dessinioti C, Paul C, Nijsten T, Gisondi P, Salavastru C, Taieb C, Trakatelli M, Puig L, *et al*: The prevalence of skin diseases in Greece, impact on quality of life and stigmatization: A population-based survey study. JEADV Clin Pract 3: 591-599, 2024.
50. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA and Yang J: 10 Years of GWAS discovery: Biology, function, and translation. Am J Hum Genet 101: 5-22, 2017.
51. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, *et al*: Finding the missing heritability of complex diseases. Nature 461: 747-753, 2009.