Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Development of Predictive Models for NB-UVB Treatment Efficacy and Safety in Psoriasis

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Background: Psoriasis is a chronic inflammatory skin disease. Narrow-band ultraviolet B (NB-UVB) phototherapy is an effective, cost-efficient, and safe treatment for plaque psoriasis; however, predictors of treatment response remain limited.

Objective: To develop predictive models for the efficacy and safety of NB-UVB phototherapy in patients with plaque psoriasis.

Methods: A total of 252 patients with plaque psoriasis were enrolled and received 12 weeks of NB-UVB phototherapy. Baseline clinical data and blood samples for genetic analysis were collected. A genome-wide association study (GWAS) was performed to identify single-nucleotide polymorphisms (SNPs) associated with treatment response and adverse events (AEs).

Results: Using a suggestive genome-wide significance threshold ($P < 1\times10^{-5}$), the *SLC7A13* rs35314286 TA allele and *DYNC1H1* rs941636 A allele showed suggestive associations with better efficacy after 4 weeks of NB-UVB treatment. Seven *ATP2B2* SNPs and ten *PSMB7* SNPs showed suggestive associations with achievement of Psoriasis area and severity index (PASI) 75 at week 12. Two *KCNA2* SNPs, seven *THSD7B* SNPs, and one *TENM4* SNP were identified as candidate markers for the occurrence of AEs.

Conclusion: Predictive models of NB-UVB treatment response in psoriasis were subsequently established and achieved area under the curve (AUC) values ranging from 0.80 to 0.85. Further validation in independent external cohorts is needed before clinical application.

Keywords: psoriasis, phototherapy, narrow-band ultraviolet B, genome-wide association study, single-nucleotide polymorphism, predictive model

Introduction

Psoriasis is a common chronic inflammatory skin disease with a burden of 125 million patients worldwide.[1] Owing to its favorable safety profile and cost-effectiveness,[2–4] narrow-band ultraviolet B (NB-UVB) phototherapy is recommended as one of the first-line treatments for psoriasis in multiple guidelines.[2,5,6] A meta-analysis demonstrated that approximately 45% to 79% of patients with psoriasis achieved 75% improvement in the psoriasis area severity index (PASI 75) following NB-UVB treatment.[7] Moreover, around 18% of patients experienced adverse reactions (AEs) during NB-UVB treatment, which included erythema, hyperpigmentation, pruritus, ultraviolet (UV) burns, pain, cutaneous lupus, gastrointestinal symptoms, and post-inflammatory hypopigmentation.[8] Proper patient selection may optimize clinical response to NB-UVB, underscoring the need for comprehensive investigation of clinical and genetic predictors, as well as the development of predictive models.

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Clinical features, which involve sex, body weight, Fitzpatrick skin type, tobacco use, and pruritus, as well as severity indicators of disease, including PASI and dermatology life quality index (DLQI), have been reported to be associated with NB-UVB treatment response.[9–12] Treatment parameters, including previous courses of NB-UVB, phototherapy regimen, cumulative NB-UVB dose, and early response to NB-UVB, may also facilitate prediction of clearance and remission duration with NB-UVB.[9,11,12] However, the presence of inconsistent findings highlights the limitations of these clinical predictors.

As the most common form of genetic variations in the human genome, single-nucleotide polymorphisms (SNPs) are widely utilized in predicting the efficacy or side effect of treatment modalities.[13,14] Few studies have been conducted in unraveling SNPs concerning NB-UVB in the management of psoriasis.[9,15,16] Vitamin D receptor (*VDR*) gene polymorphism (rs731236) is associated with long-term maintenance of phototherapeutic effect.[9] Toll-like receptor 9 (*TLR9*) gene polymorphism (rs187084) may affect PASI improvement and length of remission in response to NB-UVB therapy.[15] Patients lacking glutathione S-transferase M1 (*GSTM1*), an antioxidant enzyme protecting cells from UV-induced oxidative stress damage, are at a higher risk of erythemal skin reaction upon NB-UVB therapy.[16]

However, these studies are limited that candidate gene approaches are hypothesis-driven, and may overlook genetic variants not preselected a priori. Therefore, we performed a genome-wide association study (GWAS) to conduct an unbiased screen for SNPs associated with NB-UVB treatment response. We found multiple candidate SNPs showing suggestive associations with NB-UVB treatment response, and we constructed predictive models for NB-UVB treatment response in psoriasis based on these findings.

Materials and Methods

A prospective, multicenter clinical trial of NB-UVB phototherapy in the treatment of psoriasis was carried out in Shanghai, China. The study was approved by the institutional ethics committees. Patients with moderate-to-severe psoriasis (defined as PASI $\geq$ 5 and body surface area (BSA) $\geq$ 5%) were enrolled between October 2020 and March 2023. Detailed inclusion and exclusion criteria were listed in Table S1. All participants provided written informed consent for clinical research and data publication. NB-UVB therapy was conducted three times per week for a total of 12 weeks. Demographic information was collected, and the PASI and AEs were recorded during follow-up.

Definitions of Clinical Variables

PASI measures psoriasis severity based on both the percentage of BSA affected and the degree of redness, thickness, and scaling of plaques, and ranges from 0 to 72.[17] BSA is reported as the percentage of a patient's total skin surface affected by psoriasis, which ranges from 0 to 100%.[18] The 5-point PGA score (0: clear; 1: almost clear; 2: mild; 3: moderate; 4: severe) was used.[19] PASI 50: a ≥50% reduction in PASI score compared with baseline. PASI 75: a ≥75% reduction in PASI score compared with baseline.

Patients Grouping

Patients were stratified according to three binary outcomes: (i) whether they achieved PASI 50 at week 4, to assess early treatment response; (ii) whether they achieved PASI 75 at week 12, the most common primary efficacy endpoint in psoriasis clinical trials, to assess treatment efficacy; and (iii) whether they experienced AEs during treatment, including erythema, pruritus, pain, numbness, blistering, hyperpigmentation, desquamation and photosensitive reaction.

Genotyping

Genomic DNA was extracted from 200 μL EDTA-anticoagulated peripheral blood using the Qiagen FlexiGene DNA Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol and subsequently diluted to a uniform concentration of 50 ng/μL. All samples were genotyped using the Infinium Global Screening Array-24, version 3.0 (Genergy Bio-technology, Shanghai).

For genotype quality control, we used PLINK v1.9[20] to exclude individuals with > 5% missing data, related individuals, and samples that failed the X-chromosome sex concordance check. We also excluded SNPs with > 2% missing data, a minor allele frequency < 1%, or failing the Hardy-Weinberg equilibrium test ($P < 1\times10^{-5}$). We then used

SHAPEIT v2.r904[21] and IMPUTE2 v2.3.1[22] to phase and impute untyped SNPs using 1000 Genomes Project Phase 3 data as the reference panel. The final imputed dataset included 4,754,629 SNPs in 252 patients after filtering for imputation quality score (INFO) > 0.8, allele frequency > 1%, and missing rate < 2%.

In Silico Annotation

Candidate SNPs were functionally annotated using the Open Targets Platform (https://platform-docs.opentargets.org), a publicly available data integration resource that integrates genetic, genomic, and literature-based evidence for systemic therapeutic target identification. For each SNP, we queried the publicly available GWAS resources within the platform to identify previously reported SNP–phenotype associations.

Statistical Analysis

To delineate the baseline characteristics of patients, median values with interquartile ranges were calculated for continuous variables, and proportions with percentages were calculated for categorical variables. The Mann–Whitney *U*-test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables. Pearson correlation analysis was used to assess correlations between continuous variables. A two-sided *P*-value < 0.05 was considered statistically significant.

We used PLINK (v1.9) to perform GWAS for NB-UVB treatment efficacy and safety using multiple logistic regression with an additive genetic model, with age, sex, BMI and genetic principal component (PC) 1–4 as covariates. Regional association plots for the lead SNPs were generated using FUMA. Both the conventional genome-wide significance threshold of $P < 5\times10^{-8}$ and the suggestive threshold of $P < 1\times10^{-5}$ were evaluated. Given the exploratory nature and modest sample size, no formal correction for multiple testing (eg, Bonferroni correction or FDR adjustment) was applied. The suggestive threshold of $P < 1\times10^{-5}$ was used to prioritize candidate SNPs. Post hoc power was calculated using the Genetic Association Study (GAS) Power Calculator.

For predictive modeling, missing predictor values were imputed using median imputation. The top SNPs and clinical variables significantly associated with treatment efficacy and safety were selected to construct the predictive models. The dataset was randomly divided into a learning set (80%) and a test set (20%), and logistic regression was used to construct the predictive models, which were visualized as nomograms. Receiver operating characteristic (ROC) curves and calibration curves were used for validation. To further assess model robustness, repeated 5-fold cross-validation with 100 repeats was performed, and the cross-validated area under the curve (AUC) was reported. Statistical analyses were performed using R software (version 4.2.3).

Results

Patient Characteristics

A total of 252 Han Chinese patients with psoriasis were enrolled in this study. Of these, 220 patients completed the 12-week course of NB-UVB therapy according to the study protocol, whereas 32 patients discontinued treatment for reasons unrelated to the study, including personal schedule conflicts or relocation (n = 22), loss to follow-up (n = 7), and voluntary withdrawal requested by the participants themselves (n = 3). The descriptive analysis of the study population was shown in Table 1. For the week 4 efficacy analysis, all 252 patients were included; 103 patients (40.9%) achieved PASI 50, whereas 149 patients (59.1%) did not. For the week 12 efficacy analysis, 220 patients were included; 135 patients (61.4%) achieved PASI 75, whereas 85 patients (38.6%) did not. For the safety analysis, 75 of the 252 patients (29.8%) experienced AEs. There were no significant differences in baseline characteristics between patients groups.

Genome-Wide Association Analyses

4-week PASI 50 Response

We found that SNP rs35314286 on chromosome 8q21.13 and rs941636 on chromosome 14q32.31 showed suggestive associations with the 4-week PASI 50 response to NB-UVB therapy in our study. SNP rs35314286 was located near the

Table 1 Baseline Characteristics of Patients

Characteristic	Week 4		*P*-value	Week 12		*P*-value	AE		*P*-value
	PASI 50 Non-Responder (n = 149)	PASI 50 Responder (n = 103)		PASI 75 non-Responder (n = 85)	PASI 75 Responder (n = 135)		No AEs (n = 177)	Experiencing AEs (n = 75)	
Age	51 (36, 64)	47 (34, 63)	0.360	50 (35, 62)	52 (35, 64)	0.655	51 (35, 64)	49 (35, 62)	0.423
Duration of disease, years	11 (6, 22)	12 (6, 20)	0.607	11 (6, 23)	11 (6, 20)	0.685	11 (6, 22)	13 (6, 21)	0.762
BMI	24.4 (22.0, 27.3)	24.4 (22.2, 25.7)	0.307	24.4 (22.4, 26.5)	24.4 (22.0, 26.1)	0.484	24.7 (22.3, 26.7)	23.9 (22.2, 26.7)	0.419
Female, %	40 (26.8%)	32 (31.1%)	0.466	19 (22.4%)	47 (34.8%)	0.050	46 (26.0%)	28 (37.3%)	0.071
Smoking, %	81 (54.4%)	46 (44.7%)	0.130	48 (56.5%)	67 (49.6%)	0.323	93 (52.5%)	35 (46.7%)	0.394
Drinking, %	58 (38.9%)	33 (32.0%)	0.263	33 (38.8%)	46 (34.1%)	0.475	65 (36.7%)	30 (40.0%)	0.624
Phototherapy history, %	73 (49.0%)	51 (49.5%)	0.935	46 (54.1%)	57 (42.2%)	0.085	84 (47.5%)	39 (52.0%)	0.510
Family history, %	29 (19.5%)	21 (20.4%)	0.856	17 (20.0%)	27 (20.0%)	1.000	39 (22.0%)	20 (26.7%)	0.427
Baseline PASI	9.0 (6.6, 11.8)	8.4 (6.4, 11.7)	0.504	8.6 (6.4, 11.0)	8.6 (6.4, 11.7)	0.748	8.7 (6.5, 11.7)	7.7 (6.2, 10.2)	0.096
Baseline BSA, %	10.0 (6.6, 16.0)	9.7 (6.0, 17.5)	0.655	9.5 (6.5, 16.3)	9.7 (6.0, 18.0)	0.917	9.5 (6.5, 17.0)	8.5 (6.0, 14.2)	0.214
Baseline PGA	3.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.248	3.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.518	3.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.211

Note: Data are presented as median (interquartile range, IQR) or percentage (%).
Abbreviations: PASI, psoriasis area and severity index; AE, adverse event; BMI, body mass index; BSA, body surface area; PGA, physician's global assessment.

solute carrier family 7 member 13 *(SLC7A13*) gene. SNP rs941636 was located downstream of the dynein cytoplasmic 1 heavy chain 1 (*DYNC1H1*) gene (Tables 2 and S2, Figure S1A).

12-week PASI 75 Response

Seven ATPase, Ca^{2+} transporting, plasma membrane 2 (*ATP2B2*) SNP loci on chromosome 3p25.3 and ten proteasome 20S subunit β7 (*PSMB7*) SNP loci on chromosome 9q33.3 showed suggestive correlations with the therapeutic effect of 12-week NB-UVB treatment (Tables 2 and S3, Figure S1B).

Adverse Events

During the 12-week period of NB-UVB treatment, the total incidence of AEs was 29.8%. Two SNP loci located in the regulatory region of the potassium voltage-gated channel subfamily A member 2 (*KCNA2*) gene on chromosome 1p13.3, seven thrombospondin, type I, domain containing 7B (*THSD7B*) SNP loci on chromosome 2q22.1, and one SNP locus downstream of the teneurin transmembrane protein 4 (*TENM4*) gene on chromosome 11q14.1 emerged as suggestive signals associated with the occurrence of AEs (Tables 2 and S4, Figure S1C).

To explore the potential biological relevance of these candidate SNPs, we queried the Open Targets Platform for previously reported SNP–phenotype associations. A complete summary of these annotations is provided in Supplementary Tables S5-S7.

PC analysis showed that eigenvalues dropped sharply after PC4, supporting the use of the first four PCs to capture the major axes of genetic variation (Figure S2). Repeating the GWAS with PC1–10 instead of PC1–4 yielded highly consistent effect estimates for all top SNPs (Tables S2-S4 vs. Tables S8-10), supporting the robustness of the primary analysis. To characterize the regional association signals, LocusZoom plots were generated for the lead SNPs suggestively associated with NB-UVB treatment response and AEs. These plots showed the local association patterns and linkage-disequilibrium (LD) structure surrounding each candidate locus (Figure S3). Post hoc power calculations were performed using the GAS Power Calculator under a case-control design. Based on the observed characteristics of the associated SNPs, we evaluated two MAF settings (0.25 and 0.35) and four genotype relative risk/OR settings (1.5, 2.0, 2.5, and 3.0) (Figure S4). The analysis showed that, at the current sample size of 252, statistical power was insufficient for detecting small-effect variants but acceptable for detecting common-frequency SNPs with relatively large effects under the parameter settings observed in our study. These results indicate that the present GWAS is underpowered for small-effect variants and should be interpreted as exploratory in nature.

Table 2 Single-Nucleotide Polymorphisms Included in Prediction Models

SNP	Gene	VEP	CHR	MAF	EA	OA	OR	95% CI	SE	*P*-value
SNPs correlated with PASI 50 response at week 4										
rs35314286	SLC7A13	/	8	0.346	TA	T	2.631	1.731–3.999	0.2136	5.96E-06
rs941636	DYNC1H1	Downstream gene variant	14	0.278	A	G	3.066	1.914–4.911	0.2404	3.15E-06
SNPs correlated with PASI 75 response at week 12										
rs28772948	ATP2B2	Intron variant	3	0.3638	C	A	0.3300	0.2044–0.5329	0.2444	5.76E-06
rs10986324	PSMB7	Intron variant	9	0.3019	C	T	0.2996	0.181–0.4961	0.2573	2.81E-06
SNPs correlated with adverse effects										
rs2821550	KCNA2	Regulatory region variant	1	0.4296	G	T	2.908	1.832–4.617	0.2358	5.97E-06
rs1367128	THSD7B	Intron variant	2	0.4179	A	G	0.3148	0.1961–0.5055	0.2416	1.72E-06
rs7939185	TENM4	Downstream gene variant	11	0.2929	T	C	3.069	1.867–5.043	0.2535	9.73E-06

Abbreviations: PASI, psoriasis area and severity index; SNP, single-nucleotide polymorphism; VEP, variant effect prediction; CHR, chromosome; MAF, minor allele frequency; EA, effect allele; OA, other allele; OR, odds ratio; SE, standard error; CI, confidence interval.

Predictive Models

Previous studies have demonstrated that baseline PASI, female sex, lower BMI, and non-smoker are associated with faster or better treatment responses to NB-UVB treatment.[9,11] Therefore, these clinical features were utilized to establish the following predictive models of treatment efficacy.

A predictive model for 4-week PASI 50 efficacy was constructed using *SLC7A13* rs35314286, *DYNC1H1* rs941636 and clinical characteristics (PASI, female sex, BMI and smoking history), which was visualized by nomogram (Figure S5A). The predictive ability of this model was evaluated using a test dataset, which had an AUC of 0.81 (Figure 1A).

A predictive model for 12-week PASI 75 efficacy was constructed using *PSMB7* rs10986324 and *ATP2B2* rs28772948 together with clinical features (PASI, female sex, BMI and smoking history), which was visualized by nomogram (Figure S6A). The predictive performance of this model was evaluated using the test dataset, which had an AUC of 0.78 (Figure S6B).

It has been reported that early response to NB-UVB treatment may predict later-phase disease clearance.[11] We also noticed a significant positive correlation ($r_s = 0.401$, $P < 0.001$) between the ratio of PASI improvement at week 4 and week 12 (Figure S6E). Among patients who achieved PASI 50 at week 4, 75.0% reached PASI 75 by week 12. Hence, the 12-week efficacy predictive model was further modified by incorporating the percentage of PASI improvement at week 4, and was visualized by nomogram (Figure S6F). The predictive performance of this adjusted model yielded an AUC of 0.80 (Figure 1B).

Early studies suggested that minimum erythema dose (MED) may be influenced by sex.[23] A predictive model of NB-UVB-related AEs was constructed using female sex, *KCNA2* rs2821550, *THSD7B* rs1367128, and *TENM4* rs7939185, which was visualized by nomogram (Figure S7A). The predictive performance of this model was evaluated using the test dataset, which yielded an AUC of 0.85 (Figure 1C).

The optimal cut-off values, sensitivity, and specificity for each model are provided in Table S11. Calibration curves were close to the diagonal line of identity (Figure S5B, S6C, S6G and S7B), and decision-curve analysis showed acceptable net benefit for these models (Figure S5C, S6D, S6H and S7C). All models demonstrated good calibration (Table S12) and stable performance across cross-validation repeats (cross-validated AUCs: 0.709 for the 4-week PASI 50 model, 0.749 for the 12-week PASI 75 model, 0.775 for the 12-week PASI 75 model with 4-week response included, and 0.775 for the AE model; Table S13). No significant SNP and clinical variable showed interactions for any endpoints (all $P > 0.05$), as summarized in Supplementary Table S14.

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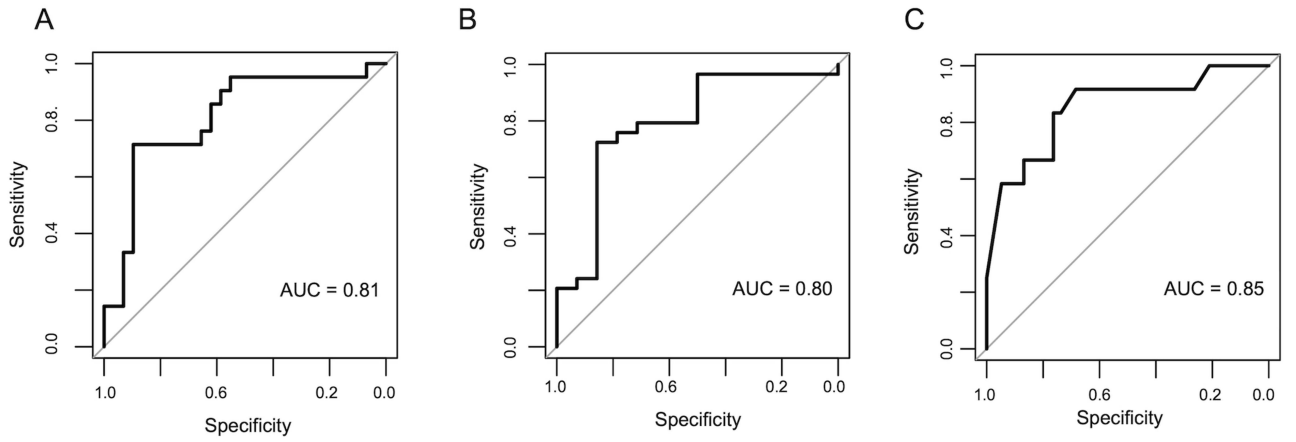

Figure 1 ROC curve of predictive models of NB-UVB treatment response in psoriasis. (**A**) ROC curve of 4-week PASI 50 response prediction model; (**B**) ROC curve of 12-week PASI 75 response prediction model in which 4-week PASI response was added as a predictor; (**C**) ROC curve of AE development prediction model.
Abbreviations: NB-UVB, narrow-band ultraviolet B; PASI, psoriasis area and severity index; AE, adverse event; ROC, receiver operating characteristic.

Discussion

Clinical characteristics have been extensively investigated for predicting NB-UVB treatment response, yet the findings remain inconsistent. An early survey showed that a history of psoriasis response to sunlight did not predict NB-UVB outcome,[24] and skin type did not significantly affect the number of exposures to clearance with NB-UVB[9] or the treatment outcome of NB-UVB.[12] In a cohort of Irish patients, female sex, lower body weight, a greater number of previous courses of NB-UVB, and lower baseline PASI or DLQI were significantly associated with fewer exposures to clearance.[9] Another study of English patients found that smoking history, higher BMI, and higher cumulative NB-UVB dose were associated with a lower PASI 90 response, whereas a higher baseline PASI score was associated with an increased PASI 90 response.[11] However, a Dutch study reported that neither baseline PASI score, smoking habits, nor alcohol consumption was associated with treatment outcome, but higher baseline itching/scratching was associated with more sessions to clearance.[12] Moreover, PASI improvement at early time points was significantly associated with PASI 75 and PASI 90 responses at the end of therapy, implying that early response to NB-UVB has a predictive value for later-phase efficacy.[11] The aforementioned study from England further developed a multivariable logistic regression model for PASI 90 response with baseline PASI, BMI, smoking status, and cumulative NB-UVB dose, which achieved an AUC of 0.80.[11] However, although the authors reported a relatively high AUC, their model relied on an on-treatment variable, cumulative dose, rather than pre-treatment clinical variables alone for prediction. Clinical features are easy and practical to assess, but inconsistent findings highlight that the prediction of NB-UVB efficacy should not rely solely on clinical characteristics.

Laboratory indicators have also been explored for predicting NB-UVB treatment response. An erythema increase greater than 53.23 arbitrary units (AU) or an increase in stratum corneum hydration of more than 1.06 AU after the first irradiation indicates that a patient may improve PASI by more than three points after fifteen NB-UVB sessions.[25] A computational model of psoriasis developed by Shmarov et al,[26] which aims to optimize phototherapy regimens through early assessment of UVB treatment response, incorporates keratinocyte and lymphocyte apoptosis rates as key parameters However, this measurement is invasive and unsuitable for clinical practice.

Limited genetic predictors have been identified for NB-UVB treatment response. HLA-C*06 carriers have been reported to show compromised effectiveness of NB-UVB therapy.[27] Patients homozygous for the C allele at VDR rs731236, which is linked with reduced VDR activity, had a shorter remission duration than those heterozygous or homozygous for the T allele.[9] However, none of the *VDR* SNPs analyzed (rs2228570, rs7975232, rs1544410, rs731236, and rs4516035) predicted the number of NB-UVB irradiation sessions required to achieve clearance.[9] In a Spanish study of 39 participants, patients with the *TLR9* rs187084 TC and CC genotype had greater PASI improvement and longer remission than those with the TT genotype.[15] Moreover, previously examined SNPs in *IL12B* (rs3212227, rs6887695),

IL23A (rs2066808), *IL-23 receptor* (*IL23R)* (rs7530511, rs2201841, rs11209026), *TLR9* (rs352140, rs5743836), *TLR2* (rs12917864, rs5743708), *TLR4* (rs4986790, rs4986791), and *TLR5* (rs5744168) had no impact on NB-UVB outcome.[15,27]

Our study did not identify any association between NB-UVB treatment response and the aforementioned genetic variations. However, our study found multiple SNPs with suggestive associations with NB-UVB efficacy. *DYNC1H1, ATP2B2*, and *PSMB7* SNPs showed suggestive correlations with NB-UVB efficacy. These SNPs may affect the level of IL-15 receptor subunit α (IL-15Rα), chemokine (C-X-C motif) ligand 9 (CXCL9), and CXCL10, as well as correlate with vitamin D deficiency. IL-15Rα is the ligand-binding chain of IL-15 receptor.[28] IL-15 belongs to the IL-2 cytokine family and has been implicated in the pathogenesis of various autoimmune diseases.[28] It has been reported to promote IL-17 secretion[29] and keratinocyte hyperproliferation.[30] UVB irradiation has been shown to upregulate IL-15 expression in keratinocytes, dermal fibroblasts, and endothelial cells.[31] CXCL9 and CXCL10 attract T lymphocytes expressing C-X-C motif chemokine receptor 3 (CXCR3) and are elevated in psoriatic skin lesions and plasma.[32–34] However, successful NB-UVB treatment does not significantly alter plasma CXCL9 and CXCL10 levels.[33] UVB irradiation inhibits interferon-γ (IFN-γ)-induced CXCL10 production in keratinocytes through mediating endoplasmic reticulum stress.[35] Keratinocytes produce vitamin D and express the vitamin D receptor (VDR),[36] and vitamin D signaling regulates keratinocyte proliferation and differentiation.[36,37] As early as 1990, an inverse correlation between 1,25-dihydroxyvitamin D and the severity of psoriatic skin lesions was identified.[38] VDR expression in psoriatic lesions is considerably lower than in non-lesional skin, and its level is negatively correlated with PASI score, disease duration, and family history.[39] Moreover, VDR ablation increases T cell production of IFN-γ and IL-17.[40] After NB-UVB therapy, serum levels of total and free 25-hydroxyvitamin D as well as VDR expression in lesional skin, are significantly increased in patients with psoriasis.[39,41,42] Our results further suggest that NB-UVB may act in part via vitamin D signaling.

Predicting NB-UVB tolerance based on Fitzpatrick skin type and MED measurement can improve treatment safety, but AEs cannot be completely avoided.[43,44] Among the AE-associated SNPs identified in our study, *KCNA2* rs2640498 may be associated with IL-18 and tumor necrosis factor receptor 2 (TNFR2) levels, *KCNA2* rs2821550 may be correlated with TNFR2 levels, and five *THSD7B* SNPs (rs1346736, rs7567733, rs7573891, rs1367128, and rs1897419) may be linked to the risk of melanoma in situ of the trunk. Mechanistically, IL-18 may protect against UV-induced keratinocyte damage by enhancing DNA repair,[45] and TNFR2 variants have been associated with sunburn tendency.[46] UV exposure is a major risk factor for melanoma development.[47] Notably, lifetime sunburns, especially during childhood, are significantly associated with increased melanoma risk.[48] Our results indicate that IL-18 and TNFR2 may affect the incidence of AEs. The correlation between sunburn and melanoma highlights the importance of preventing NB-UVB-related AEs.

The SNP-based predictive models showed high accuracy (AUC: 0.81–0.85), and may have potential clinical utility for early identification of suitable candidates for NB-UVB therapy. Although NB-UVB itself is cost-effective, it requires frequent hospital visits. A one-time SNP screening (estimated at approximately $100) could potentially reduce up to 36 visits per patient, offering both economic and clinical value.

Limitations

First, as a pilot study, the relatively modest sample size for the GWAS and the use of a suggestive threshold without formal multiple-testing correction may reduce statistical power and may potentially increase the risk of false-positive findings or overestimation of effect sizes. Although post hoc power calculations suggested reasonable power to detect common variants with relatively large effects, the study remains underpowered for low-frequency variants and common variants with small effects. Second, all participants were recruited from China, and the lack of independent external validation may limit the generalizability of our findings to other ethnic populations. Third, potential overfitting cannot be fully excluded given the modest sample size. Although cross-validated AUCs remained acceptable, they were lower than the test-set estimates. Additionally, exact times to PASI 50/PASI 75 achievement and AE onset were not systematically recorded, so time-to-event analyses could not be performed. No gene ontology (GO) or kyoto encyclopedia of genes and genomes (KEGG) pathways reached significance. No experimental validation was performed. The genetic associations identified in this study should therefore be considered exploratory signals, and both the SNP signals and the predictive

models require validation in larger, independent external cohorts. Further investigation is needed to clarify the biological pathways underlying NB-UVB treatment response.

Conclusion

Our study identified genetic polymorphisms associated with NB-UVB treatment response in psoriasis and found multiple SNP loci showing suggestive associations with efficacy and AEs. Predictive models for NB-UVB efficacy and safety with good discriminatory performance were successfully constructed. These models may serve as potentially valuable tools to advance precision medicine by identifying patients with psoriasis who are most likely to benefit from NB-UVB therapy while minimizing the risk of AEs. Given the modest sample size and absence of external replication, the identified loci should be considered exploratory and hypothesis-generating rather than definitive susceptibility loci, further validation in independent external cohorts is needed before clinical application.

Abbreviations

NB-UVB, Narrow-band ultraviolet B; GWAS, Genome-wide association study; SNPs, Single-nucleotide polymorphisms; PASI, Psoriasis area and severity index; AEs, Adverse events; AUC, Area under the curve; DLQI, Dermatology life quality index; VDR, Vitamin D receptor; TLR9, Toll-like receptor 9; GSTM1, Glutathione S-transferase M1; BSA, Body surface area; INFO, Imputation quality score; PC, principal component; GAS, Genetic Association Study; ROC, Receiver operating characteristic; SLC7A13, Solute carrier family 7 member 13; DYNC1H1, Dynein cytoplasmic 1 heavy chain 1; ATP2B2, ATPase, Ca^{2+} transporting, plasma membrane 2; PSMB7, Proteasome 20S subunit β7; KCNA2, Potassium voltage-gated channel subfamily A member 2; THSD7B, Thrombospondin, type I, domain containing 7B; TENM4, Teneurin transmembrane protein 4; MED, Minimum erythema dose; AU, Arbitrary units; IL23R, IL-23 receptor; IL-15Rα, IL-15 receptor subunit α; CXCL9, chemokine (C-X-C motif) ligand 9; HaCaT, human keratinocyte; CXCR3, C-X-C motif chemokine receptor 3; IFN-γ, interferon-γ; TNFR2, tumor necrosis factor receptor 2; GO, Gene ontology; KEGG, Kyoto encyclopedia of genes and genomes.

Data Sharing Statement

Data are accessible in NODE (https://www.biosino.org/node) with the accession number OEZ00021932, or through the URL: https://www.biosino.org/node/analysis/detail/ OEZ00021932.

Ethics Approval and Informed Consent

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for the use of clinical data was granted by the Medical Ethical Committee of Shanghai Skin Disease Hospital (approval #2020-36), Ethics Committee of Shanghai Changhai Hospital (approval #2020-27), Ethics Committee of Shanghai Sixth People's Hospital (approval #2020-KY-047K) and Ethics Committee of Shanghai Tenth People's Hospital (approval #20KT110). Trial registration was approved by Chinese clinical trial registry (approval #ChiCTR2000036186, registration date: 2020-08-21, URL: https://www.chictr.org.cn/showproj.html?proj=58256). The patients in this manuscript have given written informed consent to publication of their case details.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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