Received: 29 August 2023 | Revised: 27 November 2023 | Accepted: 18 December 2023

DOI: 10.1111/exd.15003

Experimental Dermatology WILEY

RESEARCH ARTICLE

Association between several immune response-related genes and the effectiveness of biological treatments in patients with moderate-to-severe psoriasis

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Funding information
Davalos-Fletcher Foundation; Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Grant/Award Number: UGP-20-131

Abstract

Biological therapies are safer and more effective against psoriasis than conventional treatments. Even so, 30–50% of psoriatic patients show an inadequate response, which is associated with individual genetic heterogeneity. Pharmacogenetic studies have identified several single nucleotide polymorphisms (SNPs) as possible predictive and prognostic biomarkers for psoriasis treatment response. The objective of this study was to determine the link between several SNPs and the clinical response to biological therapies in patients with moderate–severe psoriasis. A set of 21 SNPs related to psoriasis and/or other immunological diseases were selected and analysed from salivary samples of patients ($n = 88$). Treatment effectiveness and patient improvement was assessed clinically through Relative Psoriasis Area and Severity Index (PASI), also called 'PASI response', as well as absolute PASI. Associations between SNPs and PASI factors were assessed at 3 and 12 months for every treatment category of IL-17, IL-23, IL-12&23 and TNF-α inhibitors. Multivariate correlation analysis and Fisher's exact test were used to analyse the relationship between SNPs and therapy outcomes. Several SNPs located in the *TLR2*, *TLR5*, *TIRAP*, *HLA-C*, *IL12B*, *SLC12A8*, *TNFAIP3* and *PGLYRP4* genes demonstrated association with increased short and long-term therapy-effectiveness rates. Most patients achieved values of PASI response ≥75 or absolute PASI<1, regardless of the biological treatment administered. In conclusion, we demonstrate a relationship between different SNPs and both short- and especially long-term effectiveness of biological treatment in terms of PASI. These polymorphisms may be used as predictive markers of treatment response in patients with moderate-to-severe psoriasis, providing personalized treatment.

KEYWORDS
biological drugs, PASI response, pharmacogenetics, psoriasis, psoriasis area severity index

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1 | INTRODUCTION

Psoriasis is a chronic systemic immune-mediated disease that affects 2%–3% of the general population.[1,2] Prevalence and incidence vary by population and age. Among Europeans, psoriasis primarily impacts adults rather than children, with both sexes being equally affected.[3] The majority of psoriasis cases, around 90%, are attributed to chronic plaque psoriasis, also referred to as psoriasis vulgaris. Furthermore, in approximately 6%–42% of cases, psoriasis is accompanied by psoriatic arthritis throughout a person's life.[4] Additionally, patients may experience other comorbidities like cardiovascular conditions, metabolic disorders, cancer or Crohn's disease, which significantly impact their quality of life.[5]

The cause of psoriasis remains uncertain, but it results from a combination of genetic, immunological and environmental factors that disrupt the normal functioning of epidermal cells, particularly the proliferation of keratinocytes and the development of epidermal hyperplasia. These alterations lead to the formation of thickened and inflamed scaly patches, causing discomfort and itchiness. Among these factors, it has been established that genetic variability explains about 70% of disease susceptibility.[6]

Over the past few decades, research on psoriasis has substantially advanced our understanding of the disease's pathophysiology, emphasizing the significance of the immune system and enabling the creation of secure and highly effective targeted treatments using monoclonal antibodies. Among these medications are anti-IL-17, anti-IL-12&23 and TNF-α inhibitors,[7,8] as well as anti-IL-23 drugs, which represent the most recently approved therapies for moderate-to-severe psoriasis.[9] These biological agents hinder the interaction between interleukins and their dedicated receptors, thereby suppressing IL-dependent cellular signalling and the release of proinflammatory cytokines.

The pathophysiology of psoriasis heavily relies on the involvement of T cells and cytokines. Numerous studies have indicated elevated levels of IL-2, IL-6, IL-8, IL-12, IL-17, IL-19, IL-23, IFN-γ and TNF-α in psoriasis.[7,10] This overexpression is believed to be responsible for the excessive proliferation of epidermal keratinocytes and the development, maintenance and recurrence of skin lesions. Among these interleukins, IL-12 and IL-23 hold particular importance due to their impact on T cells.[7,10] While IL-12 drives Th1 cell differentiation, IL-23 is critical for the proliferation of Th17 and Th22 cells. Th17 cells produce interleukins such as IL-17, IL-22 and TNF-α. Therefore, activation of the Th17 pathway by IL-23 is closely linked to the inflammatory processes and autoimmune responses observed in psoriasis.[11] In this regard, targeted immunomodulation through biological therapies has revolutionized the ability to manage this immune-mediated disorder.

On the other hand, large-scale genome-wide association studies (GWAS) have provided insights into the genetic underpinnings of psoriasis. These revelations have, in the last decades, paved the way for biological therapies (e.g. cyclosporine, methotrexate or acitretin) that surpass conventional systemic treatments in both efficacy and safety.[4] Specifically, these new therapies have improved the clinical symptoms and reduced the risk of developing comorbidities.

In contrast to conventional systemic medications, biologic drugs selectively target specific components of the immune system, inhibiting the activity of T cells or cytokines such as tumour necrosis factor-alpha (TNF-α), interleukins (IL) 17, IL-12 or IL-23.[12,13] According to these molecular targets, TNF-α or IL inhibitors have been developed for the treatment of psoriasis. However, patients show heterogeneity in their treatment outcomes, both short- and long-term, and some patients develop different degrees of toxicity.[14,15] The variability in treatment response is influenced by the patient's genetic makeup, specifically the presence of genetic variations that can impact therapy effectiveness and safety. This heterogeneity may affect drug metabolism, the cellular environment or the drug's mechanism of action. Hence, the identification of genetic biomarkers as predictors of treatment response becomes crucial to optimize and provide personalized treatment options. This not only reduces the likelihood of adverse effects but also enhances the overall efficiency of therapies, benefiting health systems in the process.

In this setting, pharmacogenetics becomes highly significant as it investigates how individual genes can impact drug responses. Currently, pharmacogenetic research has examined how genetic variations (SNPs) can influence the response to biological treatments and the occurrence of toxicity.[16] Among the most prevalent polymorphisms identified as predictors for treatment response are genes encoding transporters (*SLC12A8*, *PDE3A-SLCO1C1*), receptors (*TNFRSF1B*, *CD84*, *FCGR2A* and *FCGR3A*, *IL17RA*, *IL23R*, *TLR* genes, *PGLYRP4*), cytokines (*TNF*, *IL* genes, *TNFAIP3*), associated proteins (*TNFAIP3*, *LY96*, *TIRAP*, *FBXL19*, *ERAP1*), but also other genes implicated directly in the pathogenesis of psoriasis (*CDKAL1*, *CARD14*, *PTTG1*, *MAP3K1*, *ZNF816A*, *GBP6*, *CTNNA2*, *HTR2A*, *CTLA4*, *TAP1*).[14] Nevertheless, there is a current dearth of research that identifies treatment-specific genetic variations linked to sustained and successful responses over a 12-month period.

This particular study aims to unveil the correlation between SNPs and both short-term and long-term clinical outcomes of psoriasis biological therapies. The findings from this study could significantly influence clinical decision-making, leading to the administration of more personalized biological treatments to patients, thereby ensuring enhanced efficacy and, subsequently, an improved quality of life for those affected.

2 | METHODS

2.1 | Patient selection and study design

A total of 88 patients (37 females and 51 males) diagnosed with psoriasis were recruited from the Department of Dermatology of the Castellon General University Hospital, La Plana Hospital of Vila-real and Valencia General University Hospital (Spain). Inclusion criteria for patient selection were as follows: (i) patients older than 18 years diagnosed with moderate-to-severe plaque psoriasis according to the Spanish Academy of Dermatology and Venereology Psoriasis Working Group consensus document criteria[17]; (ii) patients undergoing biological treatment for psoriasis;

and (iii) patients under follow-up and monitoring for over a year (Figure 1). At diagnosis, a saliva sample was collected from each patient to perform genetic analyses. Clinical data of patients were obtained from clinical records at 3 and 12 months from the start of treatment.

Patients included in the study were classified into four groups according to the biological treatment administered: Group 1 included anti-IL-17 drugs such as Secukinumab or Ixekizumab; Group 2 included anti-IL-23 drugs such as Guselkumab and Risankizumab; Group 3 included anti-IL-23 and 12 drugs such as Ustekinumab; and Group 4 included TNF-α inhibitors such as Infliximab, Adalimumab, Etanercept or Certolizumab (Figure 1). Treatment effectiveness was evaluated by the reduction or complete remission of the skin lesions. For this, Relative Psoriasis Area and Severity Index (PASI) also called 'PASI response' was used. All patients included in the study had an initial PASI score of 4 or higher (≥4), which is the specific PASI score that was considered for moderate-to-severe psoriasis. International guidelines consider as effective '*a reduction of a PASI between baseline and a specified treatment period by at least 75% (PASI75 response)*'.[18] PASI75 has been the treatment goal for moderate-to-severe psoriasis in most clinical trials.[19] However, with the implementation of more effective biological drugs for psoriasis treatment, some authors consider that PASI90 or PASI100 should be considered as the new assessment parameters.[19]

The present study considered PASI50, PASI75 and PASI90 at 3 and 12 months from treatment onset (Figure 1). Patients with PASI50 response were classified as non-responders; patients with PASI75 as responders; and patients with PASI90 response as super-responders.[19] The latter group includes patients that present a fast and exceptional improvement with treatment. In addition to PASI response, absolute PASI<3 and PASI<1 was also collected. Absolute PASI is the most frequent score used to quantify treatment effectiveness in routine clinical practice since it indicates the status of the disease. In general, there is a consensus that absolute PASI scores of ≤3 and ≤5 represent appropriate treatment responses.[20]

The study presented here was carried out in accordance with the Declaration of Helsinki. Moreover, the protocol of the study was approved by the Ethics Committee of the Castellon General University Hospital, and all patients gave written informed consent to participate.

2.2 | Selection of genetic markers

A total of 21 psoriasis-related SNPs previously described[21,22] were chosen for analysis based on (i) promising susceptibility in psoriasis (SNPs rs3213094 and rs2546890 in *IL12B*, rs11209026 in *IL23R*, rs12191877 in *HLA-C*, rs10782001 in *FBXL19*, rs9304742 in *ZNF816A*, rs610604 in *TNFAIP3*, rs1800629 in *TNF*, rs2916205 in *PGLYRP4* and rs651630 in *SLC12A8*); (ii) relation to inflammatory or immune diseases such as rheumatoid arthritis, psoriatic arthritis and Crohn's disease among others (rs6908425 in *CDKAL1*, rs1801274 in *FCGR2A*, rs96844 in *ANKRD55*, rs11938228 in *TLR2*, rs5744174 in *TLR5*, rs1799724 in *TNF*, rs1143623 in *IL1B*, rs8177374 in *TIRAP* and rs1061622 in *TNFRSF1B*); and (iii) cell adhesion and migration

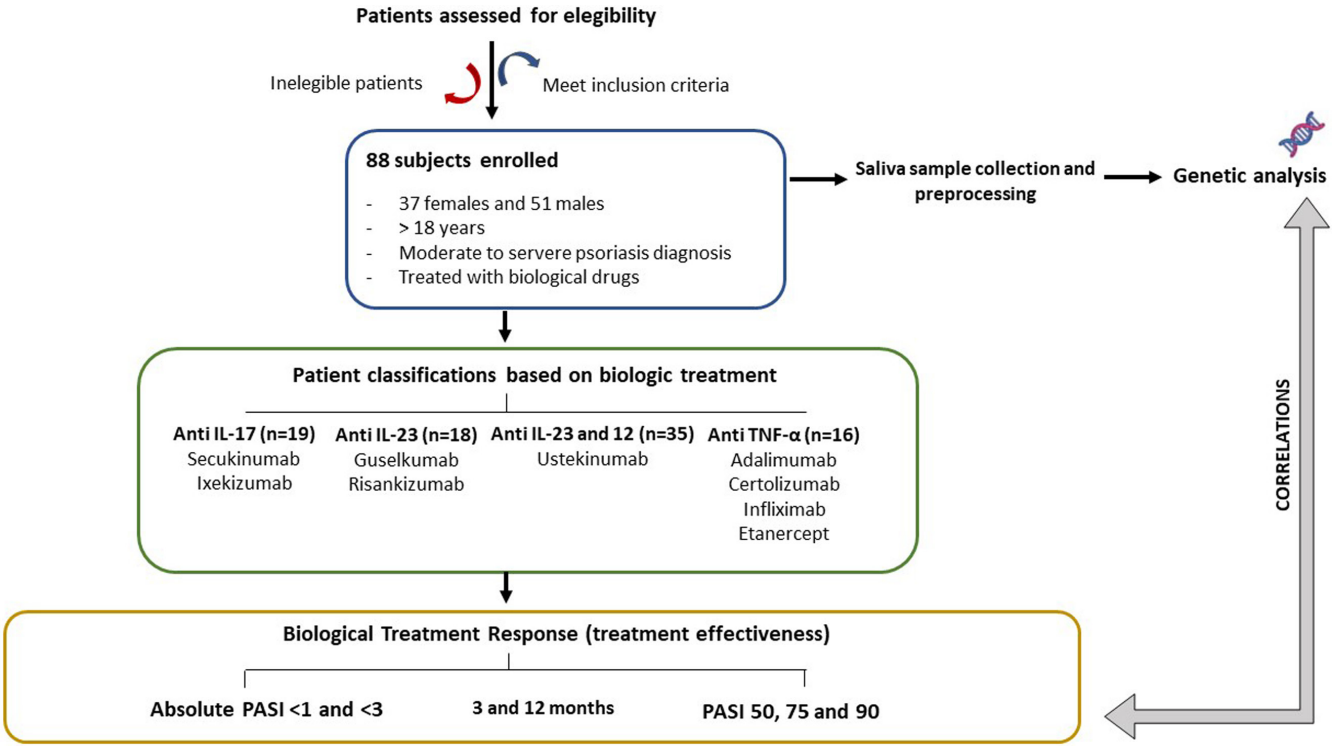

FIGURE 1 Study design.

(rs11126740 in *CTNNA2*). Online platforms such as GeneCards, PathCards, SNPedia, National Center for Biotechnology Information (dbSNP) and GWAS Catalog were used to establish the relationship between genes and SNPs to biological pathways and diseases.

2.3 | Sample processing and genotyping

A sample of saliva was collected from each patient using a sterile buccal swab. Genomic DNA was isolated from saliva samples using the QIAamp DNA mini kit (Qiagen), following the manufacturer's recommendations; and afterward, samples were stored at −80°C.

SNP genotyping was conducted by the Spanish National Genotyping Centre (CeGen-PRB2, Santiago de Compostela, Spain) as a contract service, as previously described.[23] Briefly, SNP genotyping was achieved by using the iPLEX Gold MassARRAY technology, according to manufacturer's protocol (Sequenom). Assays were implemented in 384-well plates, together with a negative control and three Coriell samples for quality control. Genotyping accuracy was also assessed by adding three DNA duplicates per plate, producing 100% consistent replication outcomes.

2.4 | Statistical analysis

Data were analysed using the R software, version 4.2.3 (http://www.R-project.org). SNPs deviations and genotype frequencies were tested for all the bi-allelic SNP markers using a Hardy–Weinberg equilibrium (HWE) test. Only the SNPs which allele frequencies were in HWE were included.

The associations between the SNPs and the other variables were performed using the R-package SNPassoc program (version 2.1–0). Every SNP was tested for all genetic models of inheritance considering a p-value <0.05 as statistically significant. All association tests were performed adjusting each SNP by covariates, sex, obesity, age at onset and years since diagnosis.

To assess differences among the variables and type of treatment groups, Pearson's chi-squared test and Fisher's exact test were used. Statistical significance was set at p-value ≤0.05.

Unknown values were excluded at each specific analysis.

3 | RESULTS

3.1 | Patient and treatment characteristics

A total of 88 patients (37 females and 51 males) diagnosed with plaque psoriasis were enrolled in this study. All recruited patients were of European Spanish descent. The average age of psoriasis onset was 26 years, and the mean duration from disease diagnosis to the present time was 23 years. A majority of patients had generalized lesions (54.12%), but others only showed lesions in specific areas of the body such as the head, elbows or limbs (45.88%). Approximately 72% of patients were overweight or obese according to OMS criteria (BMI > 25 or 30, respectively), 15% were smokers, and 50% had family history of psoriasis. Among the patients, 29% had additional comorbidities associated with the immune system, with psoriatic arthritis being particularly notable, concurrent with psoriasis in 23% of the cases (Table S1).

Regarding treatment, 79 patients (91%) had been previously treated with single or combined systemic treatment (e.g. methotrexate, cyclosporine, methotrexate/cyclosporine and acitretin); 36 patients (48%) had already undergone a first line of biological treatment for psoriasis; and the remaining 42 patients (52%) were naive regarding biological treatment. Patient and treatment characteristics are described in Table S1.

3.2 | Clinical outcomes of biological treatments

3.2.1 | Anti-IL-17

A total of 13 patients were treated with Secukinumab as first biological treatment option, and 6 as the second therapeutic option. Only one patient was treated with Ixekizumab as a second biological treatment. At 12 months of treatment, 53% of patients achieved an absolute PASI<1 and 18% a PASI<3. If treatment response is analysed according to PASI response, 24% of patients were non-responders, 6% were responders, and 56% were super-responders (Table 1).

3.2.2 | Anti-IL-23

Out of 14 patients, 13 received Guselkumab as their second biological treatment, while 2 out of 4 patients were administered Risankizumab as their second-line option. The 12-month effectiveness results indicated that 67% of patients achieved PASI<1, and 33% attained PASI<3. Remarkably, 82% of the total group were classified as super-responders (Table 1).

3.2.3 | Anti-IL-12 & IL-23

This group of patients was treated with Ustekinumab, with 54% of them receiving it as a second-line treatment. After 12 months of treatment, 48% of patients attained a PASI<1. The PASI response analysis revealed that 59% were classified as super-responders, 16% as responders, and 22% as non-responders (Table 1).

3.2.4 | Anti-TNF-α

The final cohort of patients received treatment with TNF-α inhibitors, namely Infliximab, Adalimumab, Etanercept or Certolizumab. Among them, 62% received this as their initial treatment option. After 12 months of treatment, 36% of patients achieved a PASI<1,

TABLE 1 Clinical response of patients to treatments based on PASI.

	Biological treatment			
	Anti-IL-17 $n=19$	Anti-IL-23 $n=18$	Anti-IL-12&23 $n=35$	TNF-α $n=16$
Absolute PASI				
PASI <3				
3 months	4/18 (22%)	3/15 (20%)	5/30 (17%)	4/15 (27%)
12 months	3/17 (18%)	6/18 (33%)	10/33 (30%)	6/14 (43%)
PASI <1				
3 months	9/18 (50%)	9/15 (60%)	18/30 (60%)	6/15 (40%)
12 months	9/17 (53%)	12/18 (67%)	16/33 (48%)	5/14 (36%)
PASI response				
Non responder				
3 months	3/18 (17%)	3/15 (20%)	6/29 (21%)	1/14 (7%)
12 months	4/16 (24%)	2/17 (12%)	7/32 (22%)	2/13 (15%)
Responder				
3 months	5/18 (28%)	1/15 (7%)	2/29 (7%)	4/14 (29%)
12 months	1/16 (6%)	1/17 (6%)	5/32 (16%)	4/13 (31%)
Super responder				
3 months	9/18 (50%)	10/15 (67%)	20/29 (69%)	6/14 (43%)
12 months	9/16 (56%)	14/17 (82%)	19/32 (59%)	6/13 (46%)

Note: For each patient, both absolute PASI score and PASI response were calculated. The total n for each treatment category reflects the total number of patients treated with that specific biological. For each treatment category, all patients are classified as early (3 months) or late (12 months) responders, regarding absolute PASI; or non-responders, responders or super-responders regarding PASI response.

and an encouraging 77% showed a positive response to the treatment, comprising responders (31%) and super-responders (46%) (Table 1).

3.3 | Genetic polymorphisms and clinical response

A total of 15 out of all 21 selected SNPs showed statistically significant associations for clinical response to one or more biological treatments at 3 and 12 months of treatment: rs10782001, rs11938228, rs1800629, rs1801274, rs2546890, rs5744174, rs610604, rs651630, rs96844, rs9304742, rs1799724, rs1143623, rs12191877, rs8177374 and rs2916205.

In Table 2, we present the SNPs associated with improved clinical outcomes in relation to PASI<1 and PASI90 after 3 and 12 months of commencing treatment. These time points were selected to evaluate early and enduring treatment responses, respectively.

Certain SNPs, including rs11938228 (*TLR2*), exhibited associations with both PASI<1 and PASI90, indicating a favourable clinical response across various treatments with highly significant *p*-values (**$p \leq 0.01$; ***$p \leq 0.0001$; see Table 2). Nonetheless, there were other SNPs that were treatment-specific. For instance, rs1143623 (*IL1B*), rs12191877 (*HLA-C*) and rs8177374 (*TIRAP*) were specific to TNF-α inhibitors, rs2916205 (*PGLYRP4*) for anti-IL-12&23, and rs9304742 (*ZNF816A*) and rs1799724 (*TNF*) for anti-IL-17 treatments (Table 2).

The rs2916205 SNP demonstrated a strong association with enduring clinical responses to IL-12&23 treatment, as evidenced by a highly significant p-value (***$p \leq 0.0001$; Table 2). Additionally, rs5744174 exhibited a correlation with TNF-α inhibitors and anti-IL-23 treatments, while rs610604 was related to TNF-α inhibitors and anti-IL-17 treatments. Conversely, rs9304742 and rs1800629 were linked to early clinical responses in patients undergoing anti-IL-17 treatments.

Out of all 15 significant SNPs, a total of eight demonstrated significant associations with sustained clinical outcomes at the 12-month mark. These include SNPs located in the *TLR2*, *TLR5*, *IL12B*, *TNFAIP3*, *SLC12A8*, *HLA-C*, *TIRAP* and *PGLYRP4* genes. Detailed information about these SNPs, such as their functions, related diseases, associated drugs and involvement in cellular pathways, can be found in Table S2. Additionally, their contribution to psoriasis pathogenesis is discussed in the following section.

4 | DISCUSSION

Research on psoriasis has significantly advanced our understanding of its pathophysiology, highlighting the role of the immune system and leading to the development of secure and effective targeted

TABLE 2 *P*-values of the significant SNPs associated with clinical responses to different psoriasis treatments at 3 and 12 months.

		PASI <1								PASI 90					
		IL-17		TNF-α		IL-23		IL-12&23		IL-17		TNF-α		IL-12&23	
Gene	SNP	3 months	12 months	3 months	12 months	3 months	12 months	3 months	12 months	3 months	12 months	3 months	12 months	3 months	12 months
FBXL19	rs10782001			1.94E-03	9.09E-04							1.77E-03			
TLR2	rs11938228	1.46E-05	3.71E-03	1.74E-03	4.32E-02		4.18E-02			1.44E-05	1.78E-04	1.99E-03			2.34E-02
TNF	rs1800629	3.63E-02								3.73E-02					
FCGR2A	rs1801274			1.91E-03	4.08E-03							2.27E-03			
IL12B	rs2546890			1.97E-03	9.29E-04							1.75E-03			
TLR5	rs5744174				9.11E-04		1.43E-02								
TNFAIP3	rs610604				8.44E-04						4.07E-02				
SLC12A8	rs651630	5.54E-03		2.07E-03	9.57E-04					5.47E-03	5.52E-03	1.71E-03			
ANKRD55	rs96844						3.38E-02								
ZNF816A	rs9304742	4.99E-02								4.90E-02					
TNF	rs1799724														
IL1B	rs1143623			2.10E-03								1.94E-03			
HLA-C	rs12191877			1.80E-03	8.70E-04							2.14E-03			
TIRAP	rs8177374			2.11E-03	8.48E-04							1.79E-03			
PGLYRP4	rs2916205								7.26E-04						6.14E-04

Note: PASI90 anti-IL-23 treatment column is missing because significant data were not observed at PASI90. Genes of SNPs related to best and durable clinical responses are indicated in bold. Only significant p-values are shown.

treatments using monoclonal antibodies. These include anti-IL-17, anti-IL-12&23, TNF-α inhibitors[7,8] and the recently approved anti-IL-23 drugs for moderate-to-severe psoriasis.[9] These biological agents suppress proinflammatory cytokines by blocking interleukins and their receptors.

In this study, the best efficacy rates of treatment were achieved with the anti-IL-23 treatment. Approximately 67% and 100% of patients attained a PASI<1 and PASI<3 respectively, and 82% were classified as super-responders (PASI≥90). On the other hand, patients who received anti-IL-17 or anti-IL-12&23 treatments exhibited comparable therapeutic effectiveness results. Around 50% of patients showed PASI values <1 and more than 70% of patients achieved a PASI<3. PASI75 and PASI90 were reached for 62% and 59% of patients on anti-IL-17 treatment, and 75% and 59% on anti-IL-12&23, respectively. Finally, a representative percentage of patients treated with TNF-α inhibitors attained a PASI<3 (79%), 77% achieved PASI75, and 46% reached PASI90 after 12 months of treatment.

These results are largely in agreement with data provided by various clinical trials. For example, at Week 50, the reported PASI90 response in studies RESTORE and REVEAL was 45% for Infliximab and 50% for Adalimumab at 3 years.[24,25] Regarding Ustekinumab, the PHOENIX 1 study reported a 5-year PASI90 response rate of 39.7%.[26] At Week 52, around 60% of the patients treated with Secukinumab achieved a PASI90 response[27]; and finally, phase III trials of Guselkumab, VOYAGE 1 and 2, provided good efficacy and safety profiles of this drug. Specifically, at 48 weeks, PASI90 response rate was achieved by 76.3% of patients.[28,29] In addition, studies such as ECLIPSE demonstrated clinical superiority of Guselkumab vs Secukinumab in long-term efficacy based on PASI90,[30] and others like the NAVIGATE showed Guselkumab superiority vs Ustekinumab.[31] Ultimately, several studies have demonstrated the safety and efficacy of Risankizumab, as well as the impressive response rates at Week 52 in terms of PASI90 and PASI100 (85.5% and 60% of patients, respectively.[32,33] These clinical outcomes reveal the durable treatment efficacy and the benefits that these biological drugs have provided to patients with moderate-to-severe psoriasis.

However, patients present biological treatment response heterogeneity due to genetic variability. Consequently, new pharmacogenetic biomarkers linked to treatment effectiveness are required to carry out personalized medicine. Our study was designed to identify associations between multiple SNPs and biological treatment response in patients with moderate-to-severe psoriasis. The performed analyses showed very significant statistical associations between several SNPs and PASI<1 and PASI90 values (as measures of good treatment effectiveness) at 3 and 12 months after treatment onset. Among them, those related to *TLR2*, *TLR5*, *IL12B*, *TNFAIP3*, *SLC12A8*, *HLA-C*, *TIRAP* and *PGLYRP4* genes were the most significant in the maintenance of long-lasting clinical responses in psoriatic patients treated with biological agents.

There are no described functional studies in the scientific literature for any of the 15 significant SNPs reported in this work. However, only three of them code for exonic variants, all missense: rs1801274 (p.H167R amino acid change) in the *FCGR2A* gene, rs5744174 (p.F616L change) in *TLR5* and rs8177374 (p.S180L change) in *TIRAP*. Their effect could indeed be due to the change in the protein they code for. In addition, five of the SNPs lie in regulatory sequences upstream of their genes: rs2546890 in the *IL12B* gene, rs1800629 and rs1799724 in *TNF*, rs1143623 in *IL1B* and rs96844 in *ANKRD55*. Out of all five variants, only the latter one (rs96844) is located within a described gene enhancer. Their effect could be conveyed by up- or down-regulating the expression of the gene. Finally, the rest of the SNPs (seven in total) are intronic variants that might be involved in alternative splicing or can influence gene expression in several different ways.

The toll-like receptors (TLRs) are crucial for recognizing pathogen-associated molecular patterns (PAMPs) and activating inflammatory responses.[34] Psoriatic plaques have elevated TLR levels (TLR1, 2, 4, 5 and 9), linked to disease exacerbation. TLR2 induces proinflammatory genes in psoriatic keratinocytes. Therefore, TLRs antagonism is used for the treatment of diseases such as psoriasis.[35] In fact, previous studies have reported how Adalimumab modulates TLR expression and improves clinical outcomes.[36] Our data also showed high significant associations between both *TLR2* rs11938228 and *TLR5* rs5744174 polymorphisms, and PASI90 and PASI<1 values, specifically for the TNF-α and IL-17 treatments. These data suggest a close association between these genetic variants and clinical outcomes achieved after treatment.

Related to *TLR* is the *TIRAP* gene, which encodes a protein that interferes with the TLR2 and TLR4 signalling cascade. Previous studies have shown that the *TIRAP* rs8177374 polymorphism modulates the immune response through reducing TLR2 signal transduction, and it was associated with UTK therapy (PASI75 at 12 weeks) (OR = 9.42, $p = 0.0051$).[37] In our study, *TIRAP* rs8177374 was significantly associated with PASI<1 at 3 and 12 months in patients treated with anti-TNF-α ($p < 0.0001$). However, previous studies did not find significant associations between and *TIRAP* rs8177374 and TNF-α therapy response.[37]

Moreover, genes as TNF-α-induced protein 3 (*TNFAIP3*) also have been linked to psoriasis through their protective role against inflammatory responses by inhibiting the NF-κβ pathway.[38] Deregulated NF-κB activation is related to several inflammatory diseases, including psoriasis. Some studies have reported that TNF-α inhibitors improve clinical outcomes and quality of life of psoriasis patients.[39,40] These data are in agreement with our results, in which the rs610604 derived allele variant, probably acting as a *TNFAIP3* enhancer, is strongly associated with a PASI<1 at 12 months in patients treated with anti-TNF-α drugs.

IL-12B is a proinflammatory cytokine that induces the Th1 pathway, related to the maintenance of Th1 memory cells and in turn associated with the IL-23A to IL-23 process. Thus, IL-12B plays an important role in the development of psoriasis.[41] The rs2546890 polymorphism in the *IL12B* gene has been previously related to psoriasis susceptibility, to the development of psoriatic arthritis in psoriasis patients, and to TNF-α treatment response.[13,22] Our studies linked

this SNP with good clinical responses to TNF-α therapy (PASI<1 and PASI90), both in the short and the long term.

The *SLC12A8* gene codes for an ion transporter related to the regulation of keratinocyte proliferation, closely implicated in psoriasis physiopathology. Previous studies have shown relationships between *SLC12A8* rs651630 polymorphism and psoriasis risk.[42] Specifically, the derived A allele of rs651630 was linked to a higher risk of paradoxical psoriasis in patients treated with TNF-α inhibitors ($p=0.011$).[13] Mirroring those results, our study finds a strong association between the ancestral G allele of rs651630 and a good clinical response (PASI<1 and PASI90) at 3 and 12 months in patients treated with anti-TNF-α and anti-IL-17.

Human leukocyte antigens (HLA) play a crucial role in recognizing exogenous proteins that trigger immune responses.[43] In our study, a significant statistical association was identified between the *HLA-C* rs12191877 polymorphism and a PASI<1 and PASI90 values at 3 and 12 months, only for patients treated with anti-TNF-α. Therefore, this polymorphism may be used as a prediction marker of good short-term and long-term response to anti-TNF-α drugs. These data align with prior knowledge regarding the significance of this SNP in psoriasis and corroborates earlier investigations.[44]

Finally, our study revealed a strong relationship between the SNP rs2916205 of the *PGLYRP4* gene and the long-term efficacy of anti-IL-12&23 treatment in psoriatic patients. The significance of this polymorphism in psoriasis and its role on the response to anti-TNF therapy has also been documented in previous research.[44] This gene encodes a peptidoglycan recognition protein involved in immune responses that bind to bacterial peptidoglycan. Consequently, an improved T-cell reaction to the bacterial antigen in psoriatic skin arises from this recognition.[45] As a result, *PGLYRP4* has been suggested as a compelling candidate gene for psoriasis.

Nonetheless, this work has limitations. While the findings are encouraging, additional studies are necessary to corroborate these indicators in more extensive patient cohorts, especially with a higher number of patients per treatment category. It is also worth noting that this research did not alter the standard clinical procedure (it is an observational study), thus lacking randomization of patients or establishing a control group. Lastly, it is important to emphasize that currently there is no genetic test available in the clinical practice to determine treatment response based on a subset of SNPs.

5 | CONCLUSION

In conclusion, we have identified several genetic polymorphisms as predictive markers of psoriasis treatment efficacy in both the short and long run. These types of studies are necessary, since patients exhibit diversity in their response to biological treatments due to genetic differences. As a result, there is a need for novel pharmacogenetic markers associated with treatment efficacy to facilitate personalized medicine.

Although these findings need validation in a larger cohort of patients, their application in clinical settings could enhance treatment optimization, achieve higher response rates, reduce side effects and costs and ultimately improve the quality of life for patients.

AUTHOR CONTRIBUTIONS

GP, LM and CM-C: Conceptualization; GP, LM, FV-C, RB-S, GP-P and AM-D: Data curation; AL, MG-B, BH, MAM-T and CM-C: Formal analysis; GP and CM-C: Funding acquisition; BH, MG-B, CM-C, GP, LH and FV-C: Investigation; AL, MG-B and BH: Methodology; GP and CM-C: Project administration; GP, LM, FV-C, RB-S, GP-P and AM-D: Resources; AL, MG-B and BH: Software; CM-C: Supervision; GP, LM, FV-C, RB-S, GP-P and AM-D: Validation; AL, MG-B, AM-D and CM-C: Writing—original draft; AL, MG-B, BH, GP, LM, FV-C, RB-S, GP-P, AM-D, MAM-T and CM-C Writing—review & editing. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

This work has been funded by the Foundation for the Promotion of Health and Biomedical Research in the Valencian Community (FISABIO), project number UGP-20-131 (given to GP and CM-C as PIs); and the Davalos-Fletcher Foundation (given to CM-C as PI). AL acknowledges her postdoctoral research contract (Margarita Salas 21-076), and MAM-T the Maria Zambrano research contract MAZ/2021/03 (UP2021-021). Both have been funded by the European Union-Next generation EU. BH's postdoctoral research contract is supported by philanthropists via the 'Amigos/as del CNIO' Programme. BH is hosted by the Centro Nacional de Investigaciones Oncológicas (CNIO), which is supported by the Instituto de Salud Carlos III and recognized as a 'Severo Ochoa' Centre of Excellence (ref. CEX2019-000891-S) by the Spanish Ministry of Science and Innovation (MCIN/AEI/10.13039/501100011033).

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1: Supporting Information.

How to cite this article: Loras A, Gil-Barrachina M, Hernando B, et al. Association between several immune response-related genes and the effectiveness of biological treatments in patients with moderate-to-severe psoriasis. *Exp Dermatol*. 2024;33:e15003. doi:10.1111/exd.15003