Received: 6 April 2024 | Revised: 2 July 2024 | Accepted: 21 July 2024

DOI: 10.1111/exd.15152

RESEARCH ARTICLE

Experimental Dermatology WILEY

Genetic polymorphisms to identify patients with an optimal response to tildrakizumab in psoriasis patients from real-life clinical practice

B. Butrón-Bris[1] | M. Llamas-Velasco[1] | M. C. Ovejero-Benito[2] | J. Santos-Juanes[3,4] | A. Martínez-López[5] | R. Ruiz-Villaverde[6] | G. Roustan[7] | O. Baniandrés[8] | R. Izu-Belloso[9] | P. de la Cueva[10] | A. Sahuquillo-Torralba[11] | A. Gónzalez-Quesada[12] | E. Vilarrasa-Rull[13] | J. Pujol-Montcusí[14] | J. García-Martínez[15] | M. Navares[16] | I. Palomar-Moreno[17] | J. Novalbos[16] | F. Abad-Santos[16] | E. Daudén[1] | H. de la Fuente[1,17]

Correspondence
H. de la Fuente, Instituto de Investigación Sanitaria Hospital de la Princesa, Diego de León 62, Madrid 28006, Spain.
Email: hortensia.fuente@salud.madrid.org

Abstract

Detecting the association of genetic variants to the response of biological therapy represents an important advance in developing a personalized therapy. The aim of this work was to study the association of polymorphisms with an optimal response to tildrakizumab in patients with psoriasis in a real-life clinical practice. Ninety patients with plaque psoriasis recruited from—Spanish hospitals receiving tildrakizumab for at least 24 weeks were genotyped for 180 polymorphisms. Optimal response to tildrakizumab was evaluated by absolute PASI ≤1 at 6 and 12 months. Polymorphisms corrected for weight and disease duration with an FDR <0.15 were included in a multiple regression model. Sixty three percent of patients achieved an absolute PASI ≤1 at 6 months, while 71% did so after 12 months. Disease duration (>27 years) and weight (>76 kg) were associated with treatment response; after correcting by these factors, no association (FDR >0.15) was found for any polymorphism and response to tildrakizumab at 6 months. The analysis at 12 months identified the genotype GG for rs610604 (*TNFAIP3*), CT for rs9373839 (*ATG5*), and delCTGT/delCTGT for rs72167053 (*PDE4D*) as risk factors to not achieve an optimal response (PASI ≤1), while CT for rs708567 (*IL17RC*) was protective, independently of weight and disease duration (FDR <0.15). The final multivariable model at 12 months showed an AUC of 0.90 (95% CI 0.82 to −0.98). We identified a set of polymorphisms that could be helpful to identify psoriatic patients with an optimal response to tildrakizumab at 12 months in real-world practice conditions.

KEYWORDS
effectiveness, genetic variants, psoriasis, tildrakizumab

*F. Abad-Santos, E. Daudén and H. de la Fuente should be considered joint senior authors.

For affiliations refer to page 6.

1 | INTRODUCTION

Psoriasis is a chronic immune-mediated skin disorder that affects approximately 2%–3% of the global population. Its aetiology involves a complex interplay between genetic, epigenetic and environmental factors. Psoriatic lesions arise from the excessive growth and abnormal maturation of epidermal keratinocytes, driven by immune mediators associated with the IL-23 and IL-17 pathways.[1]

Several biologic therapies, including tildrakizumab, a monoclonal antibody inhibiting the p19 subunit of IL-23, have been employed for the treatment of moderate-to-severe psoriasis. IL-23, produced by dendritic cells, promotes the differentiation and proliferation of Th17 cells. Th17 cells have been identified as central in driving psoriasis, activating keratinocytes, and leading to the production of pro-inflammatory mediators. This, in turn, recruits and stimulates additional inflammatory cells, establishing a positive feedback loop that perpetuates the inflammatory processes.[2] Despite the demonstrated efficacy of tildrakizumab in clinical trials,[3–5] its real-world effectiveness rates vary.[6–8]

Given the high cost of biologic therapies and the impact on patients' quality of life when there is a lack of response, it is crucial to identify predictive markers that enable personalized medicine by tailoring treatment to individual patients.[9] Due to the polygenic nature of autoimmune diseases, genetic markers, particularly single-nucleotide polymorphisms (SNPs), have been proposed as valuable tools for predicting the efficacy of biological treatments.[10]

Numerous research groups have undertaken investigations on diverse genetic polymorphisms in relation to the efficacy of biologics in psoriasis. In a comprehensive review of the subject, it is evident that existing knowledge primarily focuses on TNF blockers, including etanercept, infliximab and adalimumab, as well as the IL-12/23 inhibitor ustekinumab.[9,11,12] This emphasizes the limited scope of current research on this topic. To our knowledge, no studies have been conducted that examine the correlation between distinct polymorphisms and the response to emerging treatments such as anti-IL23 drugs.[13,14]

Traditionally, the efficacy of anti-psoriatic treatments has been evaluated based on the relative improvement from baseline PASI scores, reported as PASI75, PASI90 or PASI100. However, there has been growing interest in utilizing absolute PASI scores as a therapeutic parameter, offers a clear and standardized measure, focusing on current lesion reduction rather than relative improvements. By using absolute PASI, it becomes easier to identify super-responders (SP) and understand the true clinical impact of treatments, which is particularly important in tailoring individualized care and advancing our understanding of treatment outcomes in real-world clinical practice.[15]

In this study, our objective was to investigate the association between 180 polymorphisms in relevant psoriasis-related genes and the response to tildrakizumab in real-life clinical practice, specifically at 6 and 12 months after initiating treatment. We used an absolute PASI score of ≤1 as a parameter to assess treatment effectiveness, thereby identifying the population of patients with an optimal response to tildrakizumab.[16]

2 | METHODS

2.1 | Subjects

This is a cross-sectional study conducted at 16 dermatology centres in Spain, approved by the Ethics Committee for Clinical Research at Hospital Universitario de La Princesa (Madrid, Spain). The study encompassed a total of 90 adult patients with moderate-to-severe chronic plaque psoriasis who had previously undergone treatment with tildrakizumab in a real-world setting or were currently receiving it. Recruitment occurred from September 2020 to September 2022, following the dosing and therapeutic regimen as per the drug label recommendations (100 mg subcutaneously at Weeks 0 and 4, followed by doses administered every 12 weeks). As inclusion criteria, patients had received treatment with tildrakizumab for at least 24 weeks. Additionally, clinical data collected included information such as age, sex, weight, disease duration, prior use of systemic and biological therapies, and the presence of psoriatic arthritis. The effectiveness of tildrakizumab was assessed at 6 and 12 months, utilizing absolute Psoriasis Area and Severity Index (PASI) scores of ≤3, ≤2, ≤1 and =0.

2.2 | Sample processing and genotyping

DNA extraction was performed from 1 mL of peripheral blood using MagNA Pure LC 2.0 (Roche, Switzerland) and quantified with a NanoDrop® ND-1000 Spectrophotometer (Wilmington, USA). A custom microarray was designed, including 180 polymorphisms of relevant genes based on an extensive literature search (Table S1).

The selection of genes considered the previous research on psoriasis, the mechanism of action of different drugs, and the response to biological therapies in related inflammatory conditions such as psoriatic arthritis, Crohn's disease and rheumatoid arthritis.[17]

Genotyping was carried out using a QuantStudio 12K Flex qPCR instrument with an OpenArray thermal block (Applied Biosystems, Thermo Fisher, USA).

2.3 | Statistics

Data analysis involved the exclusion of polymorphisms with >5% missing genotypes and individuals with more than 5% missing data. The association of clinic-demographic variables, age, sex, psoriatic arthritis, disease duration and baseline PASI score (<10 vs. ≥10) with treatment effectiveness was evaluated using univariable logistic regression. SNPassoc r package was used to test the association between each polymorphism and the clinical response to tildrakizumab, each variant was tested to identify the best adjustment to the type of inheritance (codominant, dominant, recessive, overdominant or

additive), adjusted by disease duration and weight of patients using the lower Akaike information criterion (AIC). Analysis at 12 months included only patients with observed clinical data.

For multivariable logistic regression model at 12 months, we selected those variants with an FDR <0.15 after correction by disease duration and weight. Weight of patients and disease duration were dichotomized after calculating the optimal cut-off values for both variables using the predict function from R package and receiver operating characteristic (ROC) analysis. Variables were standardized to allow for direct comparison of their effects. The model was constructed using the stepwise backward selection method. Due to the presence of sparse or even zero observations in some genetic variants within one of the categories, Firth's penalized method was used for multivariable analysis.[18] Receiver operating characteristic curve analysis was conducted to evaluate the discriminative ability of models to distinguishing between responders and non-responders based on absolute PASI score. Statistical analysis was performed in RStudio version 2023.09.0+463 (http://www.rstudio.com/). Firth's logistic regression was performed in STATA 14.0 using firhlogit function from FIRTH package. See graphical abstract.

3 | RESULTS

3.1 | Baseline demographic data

A total of 90 patients were recruited, 44% male and 56% female patients, with an average age of 52.03 years. Thirteen patients (14%) had psoriatic arthritis (PsA), and the average disease duration was 23 years. The mean baseline PASI score was 11.64±7.35. Twenty-four (27%) patients were treatment-naive for biologics when they started tildrakizumab. The patients' clinical and demographic characteristics are summarized in Table 1. No significant adverse events were reported.

3.2 | Effectiveness

Regarding treatment outcomes, 81% and 87% of patients achieved an absolute PASI score of ≤3 after 6 and 12 months of treatment, respectively. At 6 months, 76% of patients achieved an absolute PASI ≤2 (SP) increasing to 81% at 12 months, 63% and 71% of individuals reached PASI ≤1 at 6 and 12 months, while 38% and 42% achieved PASI=0 at 6 and 12 months, respectively. For the present work, we have defined optimal response to tildrakizumab when patients achieve a PASI ≤1. Among patients that achieved PASI ≤1 at 6, 93% maintained the response at 12 months. Among those not achieving PASI ≤1, while 27% of those who had not achieved it, improved their response at 12 months.

3.3 | Association study

Two out of 90 patients were excluded from the association analysis because of genotyping failure, and two patients were excluded from the analysis at 12 months due to missing clinical data. Thus, the association study at 6 months included 88 patients and 86 patients at 12 months.

TABLE 1 Phenotypic characteristics of patients (baseline data).

Characteristic	*n* = 90
Male, *n* (%)	40 (44%)
Age (mean ± SD)	52.03 ± 12.46
Weight (kg), mean ± SD	79.22 ± 17.18
PsA *n*, (%), yes	13 (14%)
Disease duration (years), mean ± SD	23.04 ± 15.06
Baseline PASI	11.64 ± 7.35
cDMARDs naïve, *n* (%), yes	13 (14.44)
Biological therapy, *n* (%), yes 1 2 ≥3	39 (43%) 16 (18%) 11 (12%)

Note: Data are shown as mean and standard deviation (SD) or number.
Abbreviations: cDMARDs, conventional disease-modifying antirheumatic drugs; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis.

Univariable analysis between treatment response (PASI ≤1) and clinical-demographic variables revealed the association with the weight of patients at 6 months (p-value <0.15), while at 12 months disease progression time and weight were associated (p-value <0.15). The optimal cut-off value for weight was 76 kg and 27 years for the disease duration. There was no association between sex, psoriatic arthritis or PASI at baseline, previous biological treatment or previous use of drug-modifying antirheumatic drugs (DMARDs) and the response to treatment (Tables S2 and S3).

The association analysis at 6 months showed several polymorphisms with a p-value <0.05 after correction by weight and disease duration. However, none of them passed the cut-off value established for the multiple corrections test (FDR <0.15), (Table S4).

The analysis at 12 months of treatment showed, as did the analysis at 6 months, several variants associated ($p < 0.05$) with response to tildrakizumab and absolute PASI ≤1 after correction by weight and disease duration (Table S5). Four of them, rs610604 (*TNFAIP3*), rs9373839 (*ATG5*), rs708567 (*IL17RC*) and rs72167053 (*PDE4D*) had an FDR <0.15 (Table 2 and Table S5). The genotypes GG for rs610604 (*TNFAIP3*), CT for rs9373839 (*ATG5*) and delCTGT/delCTGT for rs72167053 (*PDE4D*) were identified as risk factors to not achieve an absolute PASI≤1, while genotype CC for rs708567 (*IL17RC*) was protective (Figure 1A, B). *PDE4D* and *IL17RC* polymorphisms were also associated with tildrakizumab response when PASI ≤3 was used as effectiveness parameter and *PDE4D* for PASI ≤2 (data not shown). *TNFAIP3*, *ATG5*, *PDE4D and IL17RC polymorphisms* were included alongside with weight of patients (>76 kg) and disease duration (>27 years) in a multivariable logistic regression model, we used the Firth's logistic regression analysis to include the polymorphisms for *PDE4D* and *IL17RC* that had no observations in one of the two study groups (Table 3). The analysis of OR values showed that weight of patients followed by disease duration is the variable with higher contribution to the risk

TABLE 2 Polymorphisms associated with an optimal response (PASI ≤1) to tildrakizumab at 12 months.

Genetic variant	Gene	Model	Risk genotype (%Resp/%non-resp)	*p*-value*	OR (95% CI)
rs610604	*TNFAIP3*	R	GG (4.9/32.0)	0.0002	14.9 (3.03–73.83)
rs9373839	*ATG5*	O	CT (16.4/44.0)	0.0007	8.27 (2.21–30.97)
rs708567	*IL17RC*	R	CC (21.3/0.00)	0.004	0.05 (0.0003–0.48)**
rs7216705	*PDE4D*	R	−/− (0.0/12.0)	0.003	41.4 (3.07–6.0e+03)**

*p-value corrected by weight and disease duration. **Firth's penalized-likelihood logistic regression calculated in R.

of not achieve a PASI≤1 at 12 m (Figure 1C). To determine the capacity of our model to discriminate between patients who could achieve or not a PASI≤1 at 12 m, ROC analysis was performed. This analysis showed that the combination of the polymorphisms for *TNFAIP3*, *ATG5*, *PDE4D* and *IL17RC* alongside weight (>76 kg) and disease duration (>27 years) has an AUC of 0.90 (95% CI 0.82–0.98), with sensitivity of 88.5% and a specificity of 83.3% to discriminate both phenotypes (Figure 2).

4 | DISCUSSION

While tildrakizumab obtained EMA approval for plaque psoriasis treatment in 2018, there is a notable absence of studies exploring the use of polymorphisms as response predictors.[19] In this study, we have identified a set of polymorphisms associated with tildrakizumab response, the collective analysis of which may serve as a valuable tool for discerning patients likely to achieve an absolute PASI score of ≤1 at 12 months in the context of real-world clinical practice.[16,19,20]

The model for PASI ≤1 at 12 months, adjusted by weight and disease duration, exhibited the most robust capacity to differentiate between responder and non-responder phenotypes. Our data also suggest that patients carrying the genotype GG for rs610604 (*TNFAIP3*), CTGT/− for rs72167053 (*PDE4D*) and CT for rs9373839 (*ATG5*) had a higher probability to not achieve PASI ≤1 after 12 months of tildrakizumab treatment, while those with CT for rs708567 (*IL17RC*) have a higher chance to have an optimal response to this treatment.

TNFAIP3 encodes for a zinc finger protein and ubiquitin-editing enzyme that inhibits NF-κB signalling pathway and TNF-meditated cell death. The results of a meta-analysis conducted in 2020 demonstrated that rs610604 was significantly associated with the risk of psoriasis.[21] Various polymorphisms in one of these genes have been linked to the response to TNFα blockers.[22] However, in the study conducted by Talamonti et al., no association was identified between the *TNFAIP3* rs610604 polymorphism and the response to ustekinumab (anti-IL-12/23).[12] Our data suggest that harbouring the GG genotype for rs610604 (*TNFAIP3*) could be useful to identify patients who will not achieve PASI≤1 at 12 months when treated with tildrakizumab. The protein encoded by autophagy-related 5 (*ATG5*) is key component of autophagy and its levels are increased in the epidermis of atopic dermatitis and psoriasis compared with healthy skin.[23] It has been previously described that patients with Crohn's disease with the CC or CT genotype for rs9373839 in ATG5 may have a higher chance to respond to adalimumab.[24] Our data suggest that psoriasis patients with the CT genotype are less probabilities to have an optimal response to tildrakizumab after 12 months of treatment onset.

cAMP is key signal transduction that regulates inflammatory responses. In inflammatory cells, enzymes of the phosphodiesterase family 4 (PDE4) play a key role in degrading cAMP.[25] Expression of mRNA PDE4D is increased in peripheral blood mononuclear cells from psoriasis and systemic lupus erythematous.[26] Inhibition of PDE4 is a therapeutic strategy for the treatment of inflammatory diseases including psoriasis.[27] In a previous work, we described the association of a genetic variant PDE4A gene with secukinumab response in psoriasis patients. That variant was associated with a higher ability to achieve an absolute PASI ≤3 at 6 months.[17] Additional polymorphisms observed in this study, including that of interleukin-17 receptor C, have been documented in the literature as being associated with an increased susceptibility to the development of conditions such as adolescent idiopathic scoliosis or Bechet's disease.[28,29] Our data demonstrated a positive association between the presence of the rs708567 polymorphism in *IL17RC* and achieving a PASI≤1 response at 12 months.

Concerning the significance observed with weight and disease duration in response to tildrakizumab, existing literature provides data affirming a substantial correlation between weight, disease duration and the efficacy of biologics. Multiple studies have illustrated that an elevated body mass index correlates with diminished responsiveness to biologic treatments, with specific evidence applicable to adalimumab and ustekinumab.[30] However, regarding disease duration, early systemic intervention, such as biologics, in the context of new-onset cutaneous psoriasis, can lead to improved clinical responses and sustained remission by preventing the development of an inflammatory disease memory.[31] Thus, it is reasonable to anticipate a better response with early initiation of anti-IL23 treatment when compared to patients with a long-standing disease.

PASI is the predominant score for appraising the severity of the disease. Nonetheless, when it comes to residual lesions, the optimal tool for assessment remains uncertain. Recent data suggest that the PGAXBSA composite could be a valuable metric for evaluating treatment effectiveness.[32] Although our analysis showed no association between baseline PASI and tildrakizumab response, the missing of PGAxBSA score is a limitation of our study.

In brief, this investigation has pinpointed a set of genetic variations linked to an optimal response to tildrakizumab, offering potential insights into its effectiveness in treating plaque psoriasis. The field of pharmacogenetic research in immune-mediated diseases,

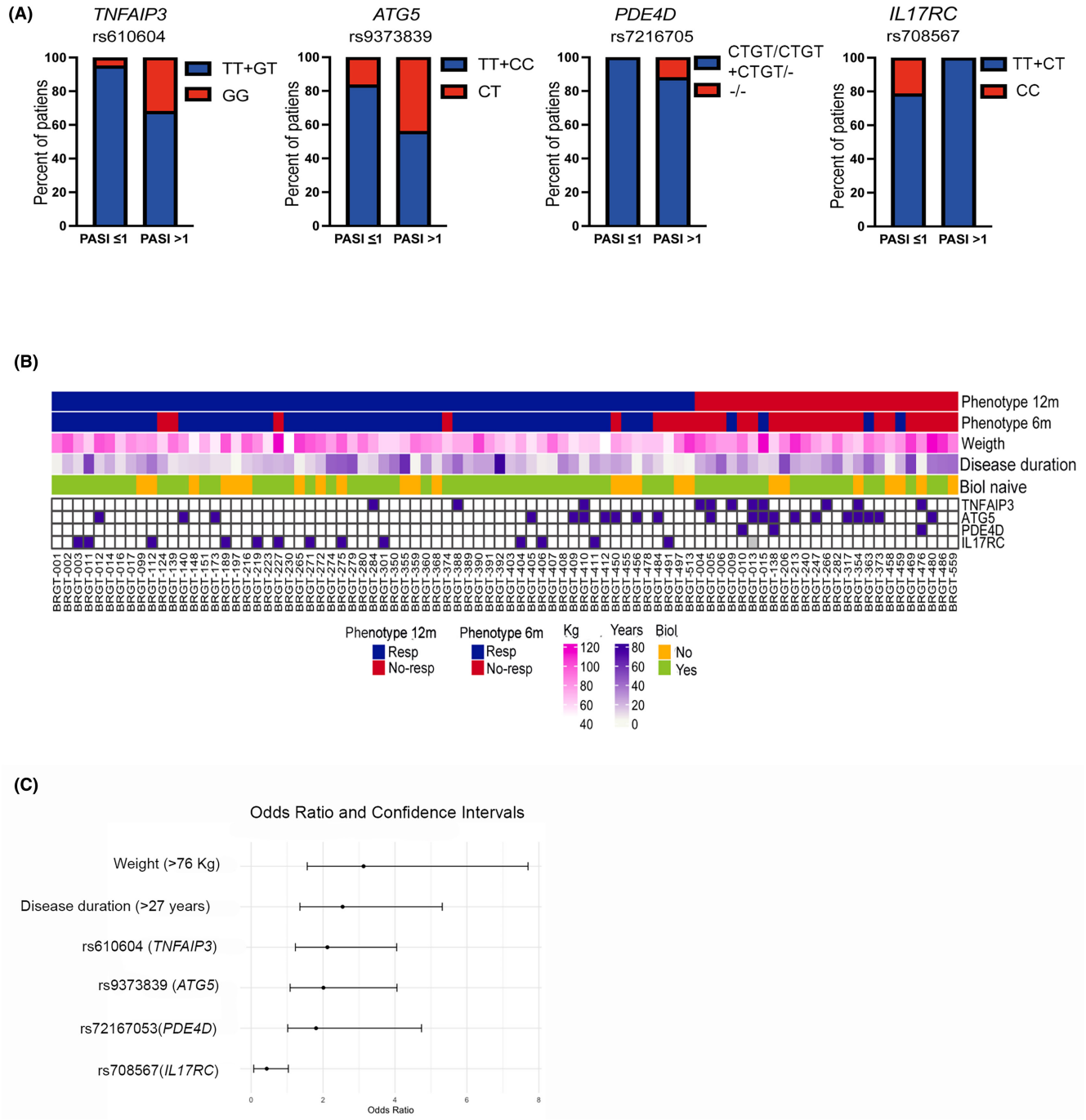

FIGURE 1 Polymorphisms in *TNFAIP3*, *ATG5*, *PDE4D* and *IL17RC* associate with an optimal response to tildrakizumab at 12 months. (A) Genotypes of *TNFAIP3*, *ATG5*, *PDE4D* and *IL17RC* in patients achieving or not an absolute PASI ≤1 at 12 months (percentages of patients with indicated genotype is shown). (B) Individual data from each patient corresponding to *TNFAIP3*, *ATG5*, *PDE4D* and *IL17RC* polymorphisms, weight, disease duration and history of biologicals. Presence of risk allele for each polymorphism is shown. Upper bars indicate responders (blue) and non-responder patients considering absolute PASI ≤1 as effectiveness parameter. (C) Odds ratio plot of standardized variables. Odds ratio and their 95% confidence intervals for the predictors included in the multivariable logistic regression model are shown.

such as psoriasis, is expanding. Nevertheless, the application of genetic markers to tailor therapies for individual patients has not yet become a standard clinical practice. This discrepancy is partly due to the variation in genetic profiles among individuals from diverse racial and ethnic backgrounds.

Despite the limitations of our study, notably the small cohort size, it is noteworthy that this study represents the inaugural pharmacogenetic work on the response to tildrakizumab in psoriasis. Further research studies are warranted to progress in this domain.

TABLE 3 Multivariate logistic regression model at 12 months.

Effectiveness parameter	Variable	Gene	Model*	Risk phenotype %resp/%nonresp	*p*-value	Odds ratio	95% CI
Absolute PASI≤1 at 12 months	rs610604	TNFAIP3	R	GG (4.9/32.0)	0.006	2.12	1.23–4.05
	rs9373839	ATG5	O	CT (16.4/44.0)	0.02	2.01	1.08–4.05
	rs708567	IL17RC	R	CC (21.3/0.00)	0.06	0.43	0.072–1.03
	rs72167053	PDE4D	R	–/– (0.0/12.0)	0.04	1.80	1.01–4.73
	Disease duration (>27 years)	–	–	–	0.003	2.54	1.35–5.31
	Weight (>76 kg)	–	–	–	0.0007	3.12	1.55–7.70

Note: Comparative group: Patients achieving indicated PASI.

Abbreviations: A, additive; C, codominant; CI, confidence interval; D, dominant; Nonresp, non-responders; O, overdominant; OR, odds ratio; PASI, Psoriasis Area and Severity Index; R, recessive; Resp, responders.

*Inheritance model.

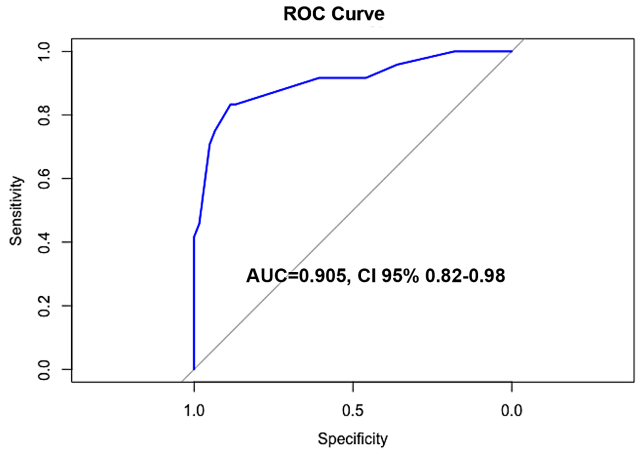

FIGURE 2 Receiver operating characteristic curve (ROC) for prediction of tildrakizumab response (absolute PASI ≤1) at 12 months based on *TNFAIP3*, *ATG5*, *PDE4D* and *IL17RC* polymorphisms, weight (>76 kg) and disease duration (>27 years).

AUTHOR CONTRIBUTIONS

B.B.-B. contributed to the manuscript preparation and database management. M.L.-V. contributed to the patient recruitment, data collection and revision of the manuscript. M.C.O.-V. contributed to the array design. J.S.-J., A.M.-L., R.R.-V., G.R., O.B., R.I.-B., P.C., A.S.-T., A.G.-Q., E.V.-R. and J.P.-M. contributed to the patient recruitment and data collection. J.G.-M. contributed to the statistical analysis. M.N. and I.P.-M. contributed to the sample processing. J.N. contributed to the data interpretation and revision of the manuscript. F.A.-S., E.D. and H.F. contributed to the conception and design, data interpretation, funding and revision of the manuscript.

AFFILIATIONS

[1]Servicio de Dermatología, Instituto de Investigación Sanitaria La Princesa, Hospital Universitario de la Princesa, Madrid, Spain
[2]Departamento de Ciencias Farmacéuticas y de la Salud, Facultad de Farmacia, Universidad San Pablo-CEU, CEU, CEU Universities Madrid, Madrid, Spain
[3]Department of Dermatology, Hospital Universitario Central de Asturias, Asturias, Spain
[4]Grupo de Investigación en Dermatología (GRIDER), Universidad de Oviedo, Oviedo, Spain
[5]Department of Dermatology, Hospital Universitario Virgen de las Nieves, Granada, Spain
[6]Department of Dermatology, Hospital Universitario San Cecilio, Granada, Spain
[7]Department of Dermatology, Hospital Universitario Puerta de Hierro, Madrid, Spain
[8]Department of Dermatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[9]Department of Dermatology, Hospital Universitario de Basurto, Bilbao, Spain
[10]Department of Dermatology, Hospital Universitario Infanta Leonor, Madrid, Spain
[11]Department of Dermatology, Instituto de Investigación Sanitaria La Fe, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[12]Department of Dermatology, Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas, Spain
[13]Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[14]Department of Dermatology, Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain
[15]Instituto de Investigación Sanitaria La Princesa, Hospital Universitario del Niño Jesús, Madrid, Spain
[16]Clinical Pharmacology Department, Instituto de Investigación Sanitaria La Princesa, Universidad Autónoma de Madrid, Hospital Universitario de La Princesa, Madrid, Spain
[17]Unit of Molecular Biology, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain

ACKNOWLEDGEMENTS

The authors would like to thank Manuel Gómez (IIS-Princesa) for editing the manuscript and the Fundación de Investigación Biomédica (FIB) administrative staff for support.

FUNDING INFORMATION

This study has been funded by Instituto de Salud Carlos III (ISCIII) through the project PI21/01583 to HF and EDT and co-funded by the European Regional Development Fund. Almirall grant from EDT. Almirall has funded this investigator-initiated study. The funding organization had no role in the design or conduct of this research.

CONFLICT OF INTEREST STATEMENT

H de la F reports grant from Instituto de Salud Carlos II, during the study; EDT reports grant from Almirall during the study, and payments from Janssen-Cilag, Leo Pharma, Almirall, Novartis, Lilly, UCB, Boehringer-Ingelheim and Bristol-Myers not related to this work. AST reports payments from AbbVie, Janssen-Cilag, Leo Pharma, Lilly, Almirall, Amgen, BMS, Novartis and Pfizer and nonfinancial support from Janssen-Cilag, Leo Pharma and Novartis, not related to this work. OBR reports payments from Janssen-Cilag, Abbvie, Pfizer, Novartis, Lilly, Celgene, Leo Pharma, Amgen, Boheringer, UCB and Almirall not related to this work. MC Ovejero-Benito has potential conflicts of interest (research support) with Leo Pharma, not related to this work. P de la C reports payments and nonfinancial support from Abbvie, Almirall, Amgen, Boehringer, Celgene, Janssen, Leo Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB not related to the submitted work. MLV reports payments from Abbvie, Almirall, Amgene, Boehringer, Celgene, Janssen, Leo Pharma, Lilly, Kyowa kirin, Novartis and UCB not related to the submitted work. Antonio Sahuquillo Torralba has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Celgene, Janssen-Cilag, LEO Pharma, Lilly, Novartis and Pfizer. FAS has been consultant or investigator in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Aptatargets, Chemo, Cinfa, FAES, Farmalíder, Ferrer, GlaxoSmithKline, Galenicum, Gilead, Italfarmaco, Janssen-Cilag, Kern, Moderna, MSD, Normon, Novartis, Servier, Silver Pharma, Teva and Zambon, but not related to this work. GR reports payments and nonfinancial support from Abbvie, Almirall, Amgen, Celgene, Janssen, Leo Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB not related to the submitted work. The rest of the authors declare do not have conflicts of interest. The rest of the authors declare do not have conflicts of interest.

DATA AVAILABILITY STATEMENT

Data of this study are available from the corresponding author upon reasonable request.

ORCID

H. de la Fuente https://orcid.org/0000-0001-8708-753X

REFERENCES

1. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet Lond Engl*. 2021;397:754-766.
2. Yang K, Oak ASW, Elewski BE. Use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis: a comprehensive review. *Am J Clin Dermatol*. 2021;22:173-192.
3. Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol*. 2015;173:930-939.
4. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet Lond Engl*. 2017;390:276-288.
5. Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *Br J Dermatol*. 2020;182:605-617.
6. Elgaard CDB, Iversen L, Hjuler KF. Guselkumab, tildrakizumab, and risankizumab in a real-world setting: drug survival and effectiveness in the treatment of psoriasis and psoriatic arthritis. *J Dermatol Treat*. 2023;34:2133531.
7. Becher G, Conner S, Ingram JA, et al. A retrospective real-world study of the effectiveness and tolerability of tildrakizumab in UK adults with moderate-to-severe chronic plaque psoriasis. *Dermatol Ther*. 2022;12:2343-2354.
8. Drerup KA, Seemann C, Gerdes S, Mrowietz U. Effective and safe treatment of psoriatic disease with the anti-IL-23p19 biologic Tildrakizumab: results of a real-world prospective cohort study in nonselected patients. *Dermatol Basel Switz*. 2022;238:615-619.
9. Ovejero-Benito MC, Muñoz-Aceituno E, Reolid A, Saiz-Rodríguez M, Abad-Santos F, Daudén E. Pharmacogenetics and pharmacogenomics in moderate-to-severe psoriasis. *Am J Clin Dermatol*. 2018;19:209-222.
10. Tavakolpour S, Darvishi M, Ghasemiadl M. Pharmacogenetics: a strategy for personalized medicine for autoimmune diseases. *Clin Genet*. 2018;93:481-497.
11. van Vugt LJ, van den Reek JMPA, Coenen MJH, de Jong EMGJ. A systematic review of pharmacogenetic studies on the response to biologics in patients with psoriasis. *Br J Dermatol*. 2018;178:86-94.
12. Talamonti M, Botti E, Galluzzo M, et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. *Br J Dermatol*. 2013;169:458-463.
13. Morelli M, Galluzzo M, Madonna S, et al. HLA-Cw6 and other HLA-C alleles, as well as MICB-DT, DDX58, and TYK2 genetic variants associate with optimal response to anti-IL-17A treatment in patients with psoriasis. *Expert Opin Biol Ther*. 2021;21:259-270.
14. Ovejero-Benito MC, Prieto-Pérez R, Llamas-Velasco M, et al. Polymorphisms associated with etanercept response in moderate-to-severe plaque psoriasis. *Pharmacogenomics*. 2017;18:631-638.
15. Mahil SK, Wilson N, Dand N, et al. Psoriasis treat to target: defining outcomes in psoriasis using data from a real-world, population-based cohort study (the British Association of Dermatologists Biologics and Immunomodulators Register, BADBIR). *Br J Dermatol*. 2020;182:1158-1166.
16. Mastorino L, Susca S, Cariti C, et al. "Superresponders" at biologic treatment for psoriasis: a comparative study among IL17 and IL23 inhibitors. *Exp Dermatol*. 2023;32:2187-2188.
17. Muñoz-Aceituno E, Butrón-Bris B, Ovejero-Benito MC, et al. Pharmacogenetic biomarkers for secukinumab response in psoriasis patients in real-life clinical practice. *J Eur Acad Dermatol Venereol*. 2023:1-8.
18. Rahman MS, Sultana M. Performance of Firth-and logF-type penalized methods in risk prediction for small or sparse binary data. *BMC Med Res Methodol*. 2017;17:33.
19. Kolli SS, Gabros SD, Pona A, Cline A, Feldman SR. Tildrakizumab: a review of phase II and III clinical trials. *Ann Pharmacother*. 2019;53:413-418.
20. Menéndez Sánchez M, Muñiz de Lucas A, Pérez Fernández E, Llamas Velasco M, Ruiz Genao DP, López Estébaranz JL. Super-responders in psoriasis under interleukin 23 inhibitor treatments, experience in two centres. *J Eur Acad Dermatol Venereol*. 2023;37:e1321-e1322.
21. Gong HB, Gao ST, Pu XM, Kang XJ, Wu XJ. Association of rs610604 in TNFAIP3 and rs17728338 in TNIP1 gene polymorphisms with psoriasis susceptibility: a meta-analysis of case-control studies. *BMC Med Genet*. 2020;21:103.

22. Tejasvi T, Stuart PE, Chandran V, et al. TNFAIP3 gene polymorphisms are associated with response to TNF blockade in psoriasis. *J Invest Dermatol*. 2012;132:593-600.
23. Klapan K, Frangež Ž, Markov N, Yousefi S, Simon D, Simon HU. Evidence for lysosomal dysfunction within the epidermis in psoriasis and atopic dermatitis. *J Invest Dermatol*. 2021;141:2838-2848.
24. Deželak M, Repnik K, Koder S, Ferkolj I, Potočnik U. A prospective Pharmacogenomic study of Crohn's disease patients during routine therapy with anti-TNF-α drug Adalimumab: contribution of ATG5, NFKB1, and CRP genes to Pharmacodynamic variability. *Omics J Integr Biol*. 2016;20:296-309.
25. Conti M, Beavo J. Biochemistry and physiology of cyclic nucleotide phosphodiesterases: essential components in cyclic nucleotide signaling. *Annu Rev Biochem*. 2007;76:481-511.
26. Schafer PH, Truzzi F, Parton A, et al. Phosphodiesterase 4 in inflammatory diseases: effects of apremilast in psoriatic blood and in dermal myofibroblasts through the PDE4/CD271 complex. *Cell Signal*. 2016;28:753-763.
27. Li H, Zuo J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Front Pharmacol*. 2018;9:1048.
28. Zhou S, Qiu XS, Zhu ZZ, Wu WF, Liu Z, Qiu Y. A single-nucleotide polymorphism rs708567 in the IL-17RC gene is associated with a susceptibility to and the curve severity of adolescent idiopathic scoliosis in a Chinese Han population: a case-control study. *BMC Musculoskelet Disord*. 2012;13:181.
29. Arıkan S, Öztürk O, Duygulu Ş, Atalay EÖ, Atalay A. Associations of IL-17 and IL-17 receptor polymorphisms with Behçet's disease in Denizli Province of Turkey. *Immunol Res*. 2023;71:600-608.
30. Karczewski J, Poniedziałek B, Rzymski P, Adamski Z. Factors affecting response to biologic treatment in psoriasis. *Dermatol Ther*. 2014;27:323-330.
31. Eyerich K, Weisenseel P, Pinter A, et al. IL-23 blockade with guselkumab potentially modifies psoriasis pathogenesis: rationale and study protocol of a phase 3b, randomised, double-blind, multicentre study in participants with moderate-to-severe plaque-type psoriasis (GUIDE). *BMJ Open*. 2021;11:e049822.
32. Gottlieb AB, Merola JF, Chen R, Levi E, Duffin KC. Assessing clinical response and defining minimal disease activity in plaque psoriasis with the physician global assessment and body surface area (PGA × BSA) composite tool: an analysis of apremilast phase 3 ESTEEM data. *J Am Acad Dermatol*. 2017;77:1178-1180.

SUPPORTING INFORMATION

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

Data S1.

How to cite this article: Butrón-Bris B, Llamas-Velasco M, Ovejero-Benito MC, et al. Genetic polymorphisms to identify patients with an optimal response to tildrakizumab in psoriasis patients from real-life clinical practice. *Exp Dermatol*. 2024;33:e15152. doi:10.1111/exd.15152