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Genome-wide association analysis of psoriasis patients treated with anti-TNF drugs

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Abstract

While anti-TNF therapies are effective against psoriasis, 30%–50% of patients do not show an adequate response to these drugs. Different candidate-gene pharmacogenetics studies have identified single nucleotide polymorphisms that may predict anti-TNF drugs response in psoriasis. Nevertheless, only one paper has undertaken a pharmacogenomic approach failing to find significant biomarkers of biological drug response along the whole genome. Furthermore, most of the pharmacogenetic candidate biomarkers identified previously have not been confirmed in a different cohort of patients. The objective of this study was to find biomarkers that could predict anti-TNF drugs response along the whole genome and validate biomarkers identified previously. A genome-wide association study (GWAS) was performed using the Human Omni Express-8 v1.2 Beadchips in 243 psoriasis patients treated with anti-TNF drugs. This study was multicentric and did not interfere with clinical practice. Associations between single nucleotide polymorphisms (SNP) and PASI75 (a 75% reduction with respect to baseline PASI) at 3 months were evaluated. Imputation was performed using SNPs with $R^2 > 0.7$. There were two SNPs located in *NPFFR2* that were close to the significant threshold of 5×10^{-8}. These data suggest that *NPFFR2* might be associated with anti-TNF drug response. However, further

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studies involving a larger cohort of patients are needed in order to confirm these results.

KEYWORDS
biological drugs, biomarkers, microarray, pharmacogenetics, pharmacogenomics, psoriasis

1 | INTRODUCTION

Psoriasis is a complex disease that affects 2%–3% of the world population.[1] This disease presents a chronic, autoimmune and inflammatory component and it is also influenced by genetic and environmental factors.[2] Apart from affecting the skin, where it generates scaly erythematous papules and plaques,[3] it can course with a wide range of comorbidities such as psoriatic arthritis, inflammatory bowel disease, cardiovascular and psychosocial conditions.[4,5] The aetiology of psoriasis is still unknown. Nevertheless, it is influenced by environmental,[6] epigenetic[7] and genetic factors.[8] Actually, previous familiar studies have demonstrated that genetic factors play a key role in the onset, development of the disease and the response of the patients to the treatment with certain drugs.[9,10] In fact, several studies have demonstrated that single nucleotide polymorphisms (SNPs) located on the following genes: tumour necrosis factor (*TNF*), interleukins 12 and 23 (IL12, IL23) and the *HLA* (Human Leukocyte Antigen)-C*0602 allele are potential risk factors in psoriasis.[11]

Biologic drugs that target TNF or its receptor (adalimumab, etanercept and infliximab) have been used as first-line biological treatment for moderate-to-severe psoriasis.[12] These treatments have demonstrated a high effectiveness and safety in clinical practice. Nevertheless, around 30%–50% of the patients do not show enough clinical improvement with these drugs.[13] Besides, although rarely, they can cause severe adverse events such as psoriasiform reactions.[14] Furthermore, biological drugs are expensive, which causes a high economic burden on national healthcare expenditures.[15] Thus, it is important to find genetic biomarkers that could help to determine which treatment is better for each patient. Although the pharmacogenetic basis of biological drug response has been widely studied in candidate-gene studies,[8,16–38] to our knowledge, there is only one publication that carried out a pharmacogenomic study in psoriasis following a hypothesis-free approach.[39] This study ($n = 65$) failed to find biomarkers predictive of drug response in a Japanese cohort of patients.[39] Therefore, the main objective of this paper was to identify pharmacogenomic biomarkers of anti-TNF drug response located along the whole genome following a hypothesis-free approach in a larger study cohort.

2 | METHODS

2.1 | Study design

The study design included a multicentric, non-interventional, observational study. This study included patients diagnosed with moderate-to-severe plaque psoriasis according to the Consensus document on the evaluation and treatment of moderate-to-severe psoriasis from the Psoriasis Group of the Spanish Academy of Dermatology and Venereology[5,40] treated with anti-TNF drugs. Eligible patients were Caucasian and older than 18 years, treated with etanercept, adalimumab or infliximab according to the doses established in the drug label and approved by the European Medicine Agency. Patients were followed in the Dermatology Department of "Hospital Universitario de La Princesa," "Hospital Universitario Central de Asturias de Oviedo" and "Hospital Universitario de Gran Canaria Doctor Negrín," Spain. Patients with other forms of psoriasis or pregnant women were excluded from this study.

The Psoriasis Area and Severity Index (PASI) was used to evaluate the effectiveness of anti-TNF drugs at 3 months of treatment. Patients were distributed in two groups being considered as responders if they achieved PASI75 (a 75% reduction of baseline PASI) at 3 months and partial or insufficiently responders if they did not achieve PASI75. The patients in this manuscript have given written informed consent to publication of their case details that allowed SNPs genotyping which fulfilled Spanish law on biomedical research and the protocol and informed consent were both approved by the Ethics Committee for Clinical Research of "Hospital Universitario de La Princesa."

2.2 | Sample processing and genotyping

A sample of 3 ml of peripheral blood was obtained from every psoriasis patient. DNA extraction was performed using the MagNa Pure® System (Roche Applied Science) and quantified in a NanoDrop® ND-1000 Spectrophotometer (Wilmington, USA). Samples were genotyped using the array Illumina HumanOmniExpressExome-8 v1.2 (Illumina) in the Center for Applied Genomics (The Children's Hospital of Philadelphia). Only samples with a DNA concentration of 50 ng/μl were included in this study.

2.3 | Quality control

A total of 964.193 SNPs were genotyped using the Illumina HumanOmniExpressExome-8 v1.2 (Illumina). All DNA samples were amplified, labelled and hybridized as stated in the Illumina Infinium Assay workflow. Bead-chip scanning was carried out with the Illumina Bead-Array reader (Illumina) Illumina´s GenomeStudio software was used to process the raw data. Downstream analysis

was performed using the software PLINK v1.07[41] following the pipeline described in.[42]

Initially, 33.234 SNPs were discarded from the analysis because they presented a percentage of missingness higher than 2% per individual.[42] Besides, 4 individuals with more than 2% of missing genotypes were excluded from the analysis[42] (Figure 1). Furthermore, a verification of X chromosome heterozygosity/homozygosity rates was performed by comparing possible differences between the real sex of the patients and the chromosomal sex of the patients.[42] No discrepancies were found between the chromosomal and the phenotypic sex of the patients. Afterwards, 24.409 SNPs were excluded from the analysis, as they were located on sex chromosomes. Only SNPs with a minor allele frequency higher than 5% were analysed, thus eliminating 322.409 SNPs. Finally, heterozygosity rate was measured, excluding 5 individuals who deviate ± 3 standard deviations from the samples' heterozygosity rate mean.[42] The final dataset is comprised of 584.141 SNPs in 182 patients (Figure 1).

2.4 | Association analysis

Statistical evaluation of the associations between individual SNP and response to anti-TNF drugs was performed using PLINK software (version 1.07; http://pngu.mgh.harvard.edu/~purcell/plink/).[41] Initially, a standard association study was carried out (Cochran-Armitage test for trend) and Fisher strand test with the PASI75 phenotype at 3 months. The results of the standard association and Fisher strand test were plotted with Manhattan with the qqman package.[43] Following the consensus for GWAS, the threshold for significance was set at 5×10^{-8} regardless of the actual SNP density of the study.[44,45]

2.5 | Imputation

Genotype imputation may further increase the number of tested associations.[42] Imputation was performed by searching common haplotypes between the genotyped patients and the following reference panel, "1,000 Genomes haplotypes -- Phase 3 integrated variant set release in NCBI build 37 (hg19) coordinates" (https://mathgen.stats.ox.ac.uk/impute/1000GP_Phase3.html).[46] Haplotypes estimation, commonly known as phasing, was performed with the software SHAPEIT v2 (r900) [47] and later imputation with the software IMPUTE2 v2.3.2.[48] Imputation was performed using SNPs with $R^2 > 0.7$. Quality control over the imputed results was accomplished following the Coleman et al 2016 protocol,[49] applying a MAF < 0.01

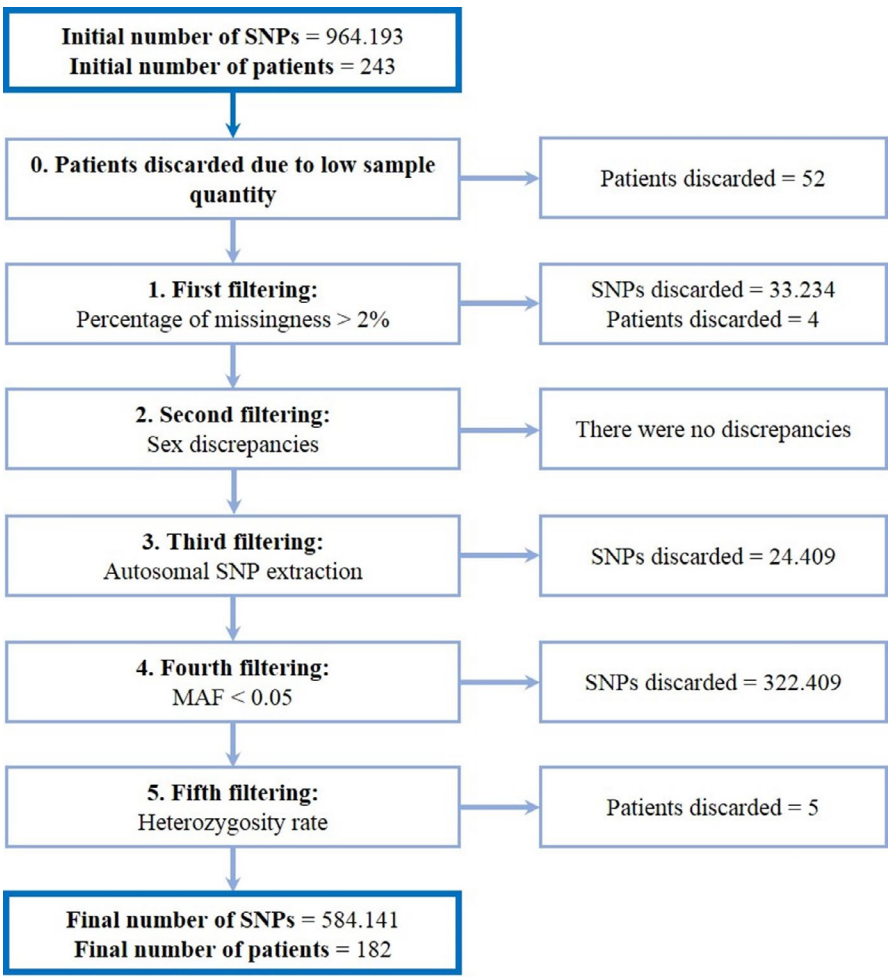

FIGURE 1 Quality control workflow applied over the genotyping data provided by the Illumina HumanOmniExpressExome-8 v1.2 array

and a percentage of missingness higher than 2% per individual. Afterwards, we performed an association study using PLINK software (version 1.9; https://www.cog-genomics.org/plink/1.9/). We followed the protocol described in the 2.4. section for the first two association analysis, and then, a principal component analysis was implemented introducing the following variables: sex, weight, age, age at onset of psoriasis, presence or absence of psoriatic arthritis, therapeutic option, and age at prescription of the first anti-TNF drug (Table 1).

2.6 | Statistical analysis

The clinical variables compared between patients with or without PASI75 included sex, weight, age, age at onset of psoriasis, presence or absence of psoriatic arthritis, therapeutic option, and age at prescription of the first anti-TNF drug. t Test and χ^2 were performed for continuous and categorical variables, respectively. SD: standard deviation. In this case, significant threshold was set at $p < .05$.

3 | RESULTS

3.1 | Study population

This study included 243 moderate-to-severe plaque psoriasis patients (99 females and 144 males). From them, 99 were treated with adalimumab; 49 with infliximab; and 95 with etanercept. The phenotypic characteristics of psoriatic patients are shown in Table 1. A total of 175 patients achieved a PASI75 response at 3 months of treatment (72.0%). As expected, there were significant differences in the patients that achieved or not PASI75 at 6 months. Apart from this variable; there were not significant differences in any demographic or clinical variable between patients who achieved PASI75 or did not achieve it (Table 1).

3.2 | SNPs associated with patients with PASI75 to biological drugs at 3 months of treatment

In order to identify SNPs associated with response, allele frequencies of 584.141 SNPs were compared between patients with or without PASI75 at 3 months. After applying Bonferroni correction, there were no SNPs with a *p*-value lower than the stated threshold for GWAS (5×10^{-8}) [44,45] (Figure 2). The SNPs that showed the strongest association with the treatment response are shown in Table 2. The threshold (5×10^{-5}) has been set according to previous GWAS that showed no significant association with biological drug response[39,50] (Table 2). The most significant SNPs are as follows: rs28461892 (*AKAP13*), rs9472377 (*SUPT3H*), rs1487419 and rs77497886 (*CDH12*), rs11037360, rs7481533, rs11037342, rs145304743 and rs1845821 (*HNRNPKP3*) (Table 2).

TABLE 1 Clinical and demographical data of the patients included in this study

	Patients (N = 243)	PASI75		Statistical significance
		Yes (*N* = 175)	No (*N* = 68)	
Age (years)	47.2 ± 14.7	47.1 ± 15.1	47.3 ± 14.0	0.944
Age at onset (years)	26.0 ± 14.5	26.0 ± 14.1	26.0 ± 15.7	0. 975
Age of the first biological drug (years)	43.5 ± 14.9	43.2 ± 15.1	44.5 ± 14.3	0.599
Females (%)	99 (40.7)	73 (73.7)	26 (26.3)	0.620
Males (%)	144 (59.3)	102 (70.8)	42 (29.2)	
Adalimumab (%)	99 (40.7)	71 (71.7)	28 (28.3)	0.816
Etanercept (%)	95 (39.1)	67 (70.5)	28 (29.5)	
Infliximab (%)	49 (20.2)	37 (75.5)	12 (24.5)	
PsA[3] (%)	154 (63.4)	113 (64.6)	41 (26.6)	0.695
Weight (kg)	77.9 ± 15.0	77.7 ± 15.1	78.6 ± 14.7	0.657
Baseline PASI	21.0 ± 11.5	20.5 ± 10.6	21.2 ± 12.1	0.816
PASI75 at 6 months (%)	167 (68.4)	150 (89.8)	17 (10.1)	0.000*

Note: Data are shown as mean ± SD or number (%).Statistical differences were analysed between patients with PASI75 (Yes) and without PASI75 (No). *t* Test and χ^2 were performed for continuous and categorical variables, respectively.

Abbreviations PsA, psoriatic arthritis; PASI, Psoriasis Area and Severity Index; SDm standard deviation.

*$P < 0.05$.

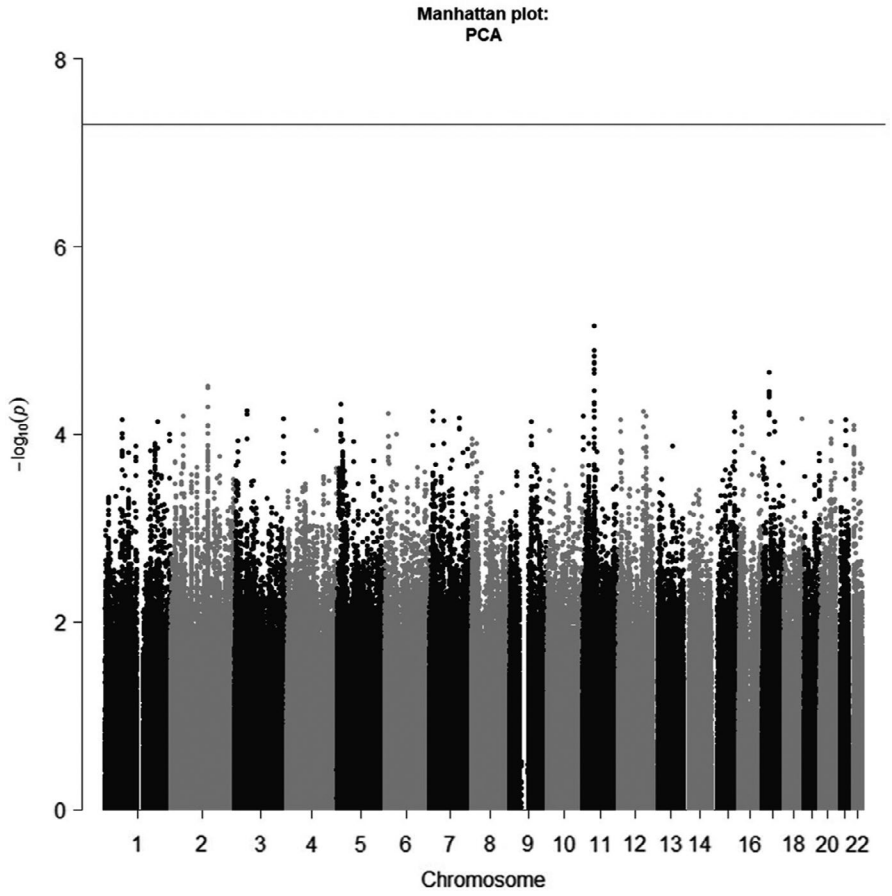

FIGURE 2 Manhattan plot of the SNPs associated with PASI75 at 3 months in the discovery cohort. This figure represents the genome-wide *p*-values from PCA (principal component analysis) between genetic variation, biological drug response and the 7 clinical variables (sex, weight, age, age at onset of psoriasis, presence or absence of psoriatic arthritis, therapeutic option and age at prescription of the first anti-TNF drug) observed in psoriasis patients. The *y*-axis shows the -log10 *p*-value of 6.612.648 SNPs, and the *x*-axis shows their chromosomal positions (SNP base pair in build GRCh37/hg19). The horizontal red line represents the genome-wide significance threshold *p*-value = 5.00×10^{-8})

TABLE 2 Summary of the SNPs showing the strongest associations (ie the smallest *p*-values) with PASI75 at 3 months of treatment for standard analysis, fisher strand test and principal component analysis. None of the polymorphisms reached the significance threshold

SNP	Chr	Location	Gene	Risk allele	*p*-value		OR (CI 95%)	
					Standard	Fisher	Standard	Fisher
rs28461892	15	86177188	*AKAP13*	A	9.43×10^{-7}	7.63×10^{-6}	7.61 (3.02–19.18)	7.61 (3.02–19.18)
rs9472377	6	44802578	*SUPT3H*	G	1.15×10^{-6}	$1.14 \times 10^{--5}$	10.61 (3.37–33.48)	10.61 (3.37–33.48)
rs1487419	5	22626115	*CDH12*	A	1.55×10^{-6}	7.96×10^{-6}	5.20 (2.52–10.74)	5.20 (2.52–10.74)
rs77497886	5	22616666	*CDH12*	T	1.55×10^{-6}	7.96×10^{-6}	5.20 (2.52–10.74)	5.20 (2.52–10.74)
rs11037360	11	43239804	*HNRNPKP3*	A	1.58×10^{-6}	4.82×10^{-6}	3.43 (2.04–5.76)	3.43 (2.04–5.76)
rs7481533	11	43223347	*HNRNPKP3*	C	3.09×10^{-6}	8.50×10^{-6}	3.34 (1.98–5.61)	3.34 (3.34–5.61)
rs11037342	11	43218424	*HNRNPKP3*	C	3.09×10^{-6}	8.50×10^{-6}	3.34 (1.98–5.61)	3.34 (3.34–5.61)
rs145304743	11	43226378	*HNRNPKP3*	T	3.09×10^{-6}	8.50×10^{-6}	3.34 (1.98–5.61)	3.34 (3.34–5.61)
rs1845821	11	43258997	*HNRNPKP3*	C	8.15×10^{-6}	1.49×10^{-5}	3.026 (1.84–4.97)	3.03 (1.84–4.97)

Abbreviations: A, adenine; *AKAP13*, a-kinase anchoring protein 13; C, cytosine; *CDH12*, cadherin 12; CHR, chromosome; CI, confidence interval; G, guanine; *HNRNPKP3*, heterogeneous nuclear ribonucleoprotein K pseudogene 3; OR, odds ratio of non-response; SNP, single nucleotide polymorphism; STMND1, stathmin domain containing 1; *SUPT3H*, SPT3 homolog, SAGA and STAGA complex component; T, thymine.

3.3 | Imputation

Imputation was performed based on the SNPs analysed in our array and the SNPs in linkage disequilibrium using 1000 Genomes haplotypes, with an overall imputation of 31.793.745 SNPs. After quality control, 25.181.097 SNPs were discarded from the dataset, with 6.612.648 SNPs remaining for the following association studies. However, no association was found between imputed SNPs and patients drug response (*p*-value $< 5 \times 10^{-8}$), either in standard and Fisher strand test or PCA (Figure 1). The following SNPs showed the strongest association with PASI75 at 3 months of treatment: rs80063785 (*CDH12*), rs13139992 and rs77656238 (*NPFFR2*) (Table 3).[44,45]

SNP	CHR	POS	GENE	RISK ALLELE	MAF	P-FREQ
rs13139992	4	73041780	*NPFFR2*	A	0.060	6.33×10^{-8}
rs77656238	4	73034261	*NPFFR2*	T	0.053	8.82×10^{-8}
rs80063785	5	22398459	*CDH12*	G	0.066	1.03×10^{-7}

Abbreviations: CHR, chromosome; CI, confidence interval; MAF, minor allele frequency, OR, odds ratio of non-response; *NPFFR2*, neuropeptide FF receptor 2. *CDH12*, cadherin 12; SNP, single nucleotide polymorphism.

*$P \leq 0.05$.

TABLE 3 Results of the frequentist analysis of the association of PASI75 at 3 months with the SNPs imputed along the whole genome. Summary of the SNP showing the smallest adjusted *p*-value with PASI75 at 3 months of treatment. None of the polymorphisms reached the significance threshold

4 | DISCUSSION

Multiple studies have been performed in order to identify new biomarkers for anti-TNF drugs in Caucasian psoriasis patie nts.[9,11,17,18,27,51–55] However, most of these biomarkers have not reached the clinical practice so far, suggesting that new and better powered pharmacogenomics studies are needed to deliver on clinically informative biomarkers for the field of psoriasis.

Although no genome-wide significant SNPs have been identified in the GWAS, some of them showed the strongest association with PASI75 at 3 months. *AKAP13*, *HNRNPKP3*, *SUPT3H* and *CDH12* are the most compelling candidate genes among our imputation results (Table 2). *AKAP13* (a-kinase anchoring protein 13) encodes for the a-kinase anchoring protein 13, which has the function of binding to the regulatory subunit of protein kinase A. A previous meta-analysis reported an association of this gene with psoriasis susceptibility.[56] However, this result was not replicated in the combined analysis (rs35343117; p-value $= 1.7 \times 10^{-6}$),[56] nor in our study (rs35343117; p-value = 0.123). The rest of SNPs is not associated with psoriasis in the literature. *HNRNPKP3* is the heterogeneous nuclear ribonucleoprotein K pseudogene with no current knowledge about its protein transcripts. The whole set of our non-significant *HNRNPKP3* SNPs are positively associated with PASI75 at 3 months. *SUPT3H* is a SPT3-like protein presumably acting as a transcriptional activator and chromatin structure regulator. Our non-significant *SUPT3H* SNPs suggest a positive association with PASI75 at 3 months. *CDH12* is a cadherin protein which SNPs are positively associated with PASI75 at 3 months.[57]

We did not uncover any SNPs significantly associated with anti-TNF drug response in Caucasian patients in our study. Our results are in agreement with a previous study carried out in 65 Japanese patients.[39] Moreover, these results are concordant with another pharmacogenomic study performed in 196 rheumatoid arthritis Caucasian patients that failed to find genetic biomarkers for anti-TNF drugs.[50] This reduced sample size, especially in the partial responders group, could partially explain the lack of biomarkers characteristic of anti-TNF drug response. On the contrary, other GWAS carried out in 96 Caucasian Crohn's disease patients [58] identified a genetic biomarker of adalimumab response (CD96) that was later confirmed in a validation cohort of 123 patients.[58]

Traditionally, we have been treating partial responders of biological drugs as a homogenous group of patients with the same genetic pathways affected. There could be different type of partial responders. It would be optimal to include patients who did not achieve PASI50 (a 50% reduction with respect to baseline PASI). However, due to the high effectiveness of these drugs, this would reduce the sample size of the non-responders group, thus reducing the statistical power of this study. Therefore, partial responders present a heterogeneous group that includes patients that did not achieve PASI50 (strictly non-responders to biological drugs) and patients that respond partially to biological drugs. Furthermore, this heterogeneity in the phenotype of the patients with a partial or poor response to biological drugs could be caused by genetic heterogeneity. This heterogeneity could be one of the causes why no significant associations with response are found in GWAS. Besides, immune system could compensate in a different way the malfunction of different proteins or signalling pathways further confounding and making it more difficult to find biomarker that predicts biological drug response. This could also explain the multiple biomarkers found in small cohorts with homogenous conditions but they could not be extrapolated to the general population.

We have found an association between two SNPs located on the *NPFFR2* (Neuropeptide FF Receptor 2) gene and anti-TNF drug response at 3 months of treatment. This gene encodes a member of a subfamily of G-protein-coupled neuropeptide receptors that is involved in pain modulation and regulation of the opioid system.[59] Although this association was not significant (p-values were 6.33×10^{-8} and 8.82×10^{-8}, Table 3) the p-values were close to the established significance threshold (5×10^{-8}).[44,45] There are two different SNPs located in the same gene that were close to this ratio. This fact reinforces the hypothesis that *NPFFR2* may be associated with biological drug response. Moreover, this gene has not been associated so far with psoriasis or biological drug response. However, further studies should be performed in order to validate this association. These type of studies may help to optimize the effectiveness of psoriasis therapy, thereby reducing the risk of adverse events, and improving precision for the patients prescribed anti-TNF therapy. Thus, more meta-analysis and studies involving larger cohorts of patients are necessary to validate the previously discovered ones in order to develop more effective and safer drugs that can be administered on a personalized basis.

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CONFLICTS OF INTERESTS

We declare the following conflicts of interests: F Abad-Santos has been a consultant or investigator in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Chemo, Farmalíder, Ferrer, GlaxoSmithKline, Gilead, Janssen-Cilag, Kern, Normon, Novartis, Servier, Teva and Zambon. E Daudén has potential conflicts of interest (advisory board member, consultant, grants, research support, participation in clinical trials, honoraria for speaking and research support) with the following pharmaceutical companies: AbbVie (Abbott), Amgen, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD, Lilly and Celgene. M Llamas-Velasco has potential conflicts of interest as she has participated in clinical trials or as consultant with Abbvie (Abbott), Galderma, Janssen-Cilag, Leo Pharma, Pfizer, Novarties, Lilly, Almirall and Celgene. MC Ovejero-Benito has potential conflicts of interest (honoraria for speaking or research support) with Janssen-Cilag and Leo Pharma. P Coto-Segura has potential conflicts of interest (advisory board member, consultant, grants, research support, participation in clinical trials, honoraria for speaking and research support) with the following pharmaceutical companies: AbbVie (Abbott), Janssen-Cilag, Novartis, Pfizer, MSD, UCB pharma, Lilly and Celgene. The other authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

AUTHOR CONTRIBUTION

MCOB wrote the paper and analysed the data. EMA, DS, BA and RP analysed the data. HH contributed essential tools. PCS, GC, AR and MLV contributed essential reagents or tools. FAS and ED designed the study, contributed essential reagents or tools and wrote the paper. Moreover, all authors have also revised the manuscript, have given approval of its final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

[1] Alwan W, Nestle FO. Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine. *Clin Exp Rheumatol*. **2015**;*33*:S2-S6.
[2] Eberle FC, Brück J, Holstein J, et al. Recent advances in understanding psoriasis. *F1000Research*. **2016**;*5*:770.
[3] Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of Psoriasis. *Annu Rev Immunol*. **2014**;*32*:227-255.
[4] Dauden E, Herrera E, Puig L, et al. Validation of a new tool to assess health-related quality of life in psoriasis: the PSO-LIFE questionnaire. *Health Qual Life Outcomes*. **2012**;*10*:56.
[5] Dauden E, Blasco AJ, Bonanad C, et al. Position statement for the management of comorbidities in psoriasis. *J Eur Acad Dermatol Venereol*. **2018**;*32*:2058-2073.
[6] Chandra A, Ray A, Senapati S, et al. Genetic and epigenetic basis of psoriasis pathogenesis. *Mol Immunol*. **2015**;*64*:313-323.
[7] Trowbridge RM, Pittelkow MR. Epigenetics in the pathogenesis and pathophysiology of psoriasis vulgaris. *J Drugs Dermatol*. **2014**;*13*:111-118.
[8] Dand N, Mahil SK, Capon F, et al. Psoriasis and genetics. *Acta Derm Venereol*. **2020**;*100*:adv00030.
[9] Prieto-Pérez R, Cabaleiro T, Daudén E, et al. Gene polymorphisms that can predict response to anti-TNF therapy in patients with psoriasis and related autoimmune diseases. *Pharmacogenomics J*. **2013**;*13*:297-305.
[10] Jiang S, Hinchliffe TE, Wu T. Biomarkers of an autoimmune skin disease—psoriasis. *Genomics Proteomics Bioinformatics*. **2015**;*13*:224-233.
[11] Prieto-Pérez R, Cabaleiro T, Daudén E, et al. Pharmacogenetics of topical and systemic treatment of psoriasis. *Pharmacogenomics*. **2013**;*14*:1623-1634.
[12] Wcisło-Dziadecka D, Zbiciak-Nylec M, Brzezińska-Wcisło L, et al. TNF-α in a molecularly targeted therapy of psoriasis and psoriatic arthritis. *Postgrad Med J*. **2016**;*92*:172-178.
[13] Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis*. **2013**;*72*:517-524.
[14] Cabaleiro T, Prieto-Pérez R, Navarro R, et al. Paradoxical psoriasiform reactions to anti-TNF? drugs are associated with genetic polymorphisms in patients with psoriasis. *Pharmacogenomics J*. **2016**;*16*:336-340.
[15] Esposito M, Gisondi P, Conti A, et al. Dose adjustment of biologic therapies for psoriasis in dermatological practice: a retrospective study. *J Eur Acad Dermatol Venereol*. **2017**;*31*:863-869.
[16] Gallo E, Cabaleiro T, Román M, et al. The relationship between tumour necrosis factor (TNF)-α promoter and *IL12B* / *IL-23R* genes polymorphisms and the efficacy of anti-TNF-α therapy in psoriasis: a case-control study. *Br J Dermatol*. **2013**;*169*:819-829.
[17] Linares-Pineda TM, Cañadas-Garre M, Sánchez-Pozo A, et al. Gene polymorphisms as predictors of response to biological therapies in psoriasis patients. *Pharmacol Res*. **2016**;*113*:71-80.
[18] Prieto-Pérez R, Solano-López G, Cabaleiro T, et al. New polymorphisms associated with response to anti-TNF drugs in patients with moderate-to-severe plaque psoriasis. *Pharmacogenomics J*. **2018**;*18*:70-75.
[19] Julià A, Ferrándiz C, Dauden E, et al. Association of the PDE3A-SLCO1C1 locus with the response to anti-TNF agents in psoriasis. *Pharmacogenomics J*. **2015**;*15*:322-325.
[20] Ryan C, Kelleher J, Fagan MF, et al. Genetic markers of treatment response to tumour necrosis factor-α inhibitors in the treatment of psoriasis. *Clin Exp Dermatol*. **2014**;*39*:519-524.
[21] Vasilopoulos V, Manolika M, Zafiriou E, et al. Pharmacogenetic analysis of TNF, TNFRSF1A, and TNFRSF1B gene polymorphisms and prediction of response to anti-TNF therapy in psoriasis patients in the Greek population. *Mol Diagn Ther*. **2012**;*16*:29-34.
[22] Coto-Segura P, Batalla A, González-Fernández D, et al. CDKAL1 gene variants affect the anti-TNF response among Psoriasis patients. *Int Immunopharmacol*. **2015**;*29*:947-949.
[23] Masouri S, Stefanaki I, Ntritsos G, et al. A pharmacogenetic study of psoriasis risk variants in a greek population and prediction of responses to anti-TNF-α and Anti-IL-12/23 agents. *Mol Diagn Ther*. **2016**;*20*:221-225.
[24] Julià M, Guilabert A, Lozano F, et al. The role of Fcγ Receptor polymorphisms in the response to anti-tumor necrosis factor

therapy in psoriasis: a pharmacogenetic study. *JAMA Dermatol*. **2013**;*149*:1033.
[25] 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.
[26] Batalla A, Coto E, Gómez J, et al. IL17RA gene variants and anti-TNF response among psoriasis patients. *Pharmacogenomics J*. **2018**;*18*:76-80.
[27] Ovejero-Benito MC, Muñoz-Aceituno E, Reolid A, et al. Pharmacogenetics and pharmacogenomics in moderate-to-severe psoriasis. *Am J Clin Dermatol*. **2018**;*19*:209-222.
[28] Tutuncu Z, Kavanaugh A, Zvaifler N, et al. Fcγ receptor type IIIA polymorphisms influence treatment outcomes in patients with inflammatory arthritis treated with tumor necrosis factor α-blocking agents. *Arthritis Rheum*. **2005**;*52*:2693-2696.
[29] van Vugt LJ, van den Reek JMPA, Coenen MJH, et al. A systematic review of pharmacogenetic studies on the response to biologics in psoriasis patients. *Br J Dermatol*. **2017**;*178*:86-94.
[30] Seitz M, Wirthmuller U, Moller B, et al. The -308 tumour necrosis factor- gene polymorphism predicts therapeutic response to TNF -blockers in rheumatoid arthritis and spondyloarthritis patients. *Rheumatology*. **2007**;*46*:93-96.
[31] Song GG, Seo YH, Kim J-H, et al. Association between *TNF-?* (-308 A/G, -238 A/G, -857 C/T) polymorphisms and responsiveness to TNF-? Blockers in spondyloarthropathy, psoriasis and Crohn's disease: a meta-analysis. *Pharmacogenomics*. **2015**;*16*:1427-1437.
[32] Chen W, Xu H, Wang X, et al. The tumor necrosis factor receptor superfamily member 1B polymorphisms predict response to anti-TNF therapy in patients with autoimmune disease: a meta-analysis. *Int Immunopharmacol*. **2015**;*28*:146-153.
[33] Ovejero-Benito MC, Prieto-Pérez R, Llamas-Velasco M, et al. Polymorphisms associated with adalimumab and infliximab response in moderate-to-severe plaque psoriasis. *Pharmacogenomics*. **2018**;*19*:7-16.
[34] 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.
[35] Ovejero-Benito MC, Muñoz-Aceituno E, Reolid A, et al. Polymorphisms associated with anti-TNF drugs response in patients with psoriasis and psoriatic arthritis. *J Eur Acad Dermatol Venereol JEADV*. **2019**; *33*:e175-e177.
[36] Ovejero-Benito MC, Muñoz-Aceituno E, Sabador D, et al. Polymorphisms associated with optimization of biological therapy through drug dose reduction in moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol JEADV*. **2020**;*34*:e271-e275.
[37] Caldarola G, Sgambato A, Fanali C, et al. HLA-Cw6 allele, NFkB1 and NFkBIA polymorphisms play no role in predicting response to etanercept in psoriatic patients. *Pharmacogenet Genomics*. **2016**;*26*:423-427.
[38] Talamonti M, Galluzzo M, Bernardini N, et al. Psoriasis Area and Severity Index response in moderate-severe psoriatic patients switched to adalimumab: results from the OPPSA study. *J Eur Acad Dermatol Venereol JEADV*. **2018**;*32*:1737-1744.
[39] Nishikawa R, Nagai H, Bito T, et al. Genetic prediction of the effectiveness of biologics for psoriasis treatment. *J Dermatol*. **2016**;*43*:1273-1277.
[40] Daudén E, Puig L, Ferrándiz C, et al. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis: Psoriasis Group of the Spanish Academy of Dermatology and Venereology. *J Eur Acad Dermatol Venereol*. **2016**;*30*:1-18.
[41] Purcell S, Neale B, Todd-Brown K, et al.PLINK: a toolset for whole-genome association and population-based linkage analysis [Internet]. **2007**. http://pngu.mgh.harvard.edu/purcell/plink/. Cited 25 Jul 2019
[42] Marees AT, de Kluiver H, Stringer S, et al. A tutorial on conducting genome-wide association studies: quality control and statistical analysis. *Int J Methods Psychiatr Res*. **2018**;*27*:e1608.
[43] Turner SD.qqman: an R package for visualizing GWAS results using Q-Q and manhattan plots. bioRxiv **2014**:005165.
[44] Reed E, Nunez S, Kulp D, et al. A guide to genome-wide association analysis and post-analytic interrogation. *Stat Med*. **2015**;*34*:3769-3792.
[45] Dudbridge F, Gusnanto A. Estimation of significance thresholds for genomewide association scans. *Genet Epidemiol*. **2008**;*32*:227-234.
[46] van Leeuwen EM, Kanterakis A, Deelen P, et al. Population-specific genotype imputations using minimac or IMPUTE2. *Nat Protoc*. **2015**;*10*:1285-1296.
[47] Delaneau O, Howie B, Cox AJ, et al. Haplotype estimation using sequencing reads. *Am J Hum Genet*. **2013**;*93*:687-696.
[48] Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLOS Genet*. **2009**;*5*:e1000529.
[49] Coleman JRI, Euesden J, Patel H, et al. Quality control, imputation and analysis of genome-wide genotyping data from the Illumina HumanCoreExome microarray. *Brief Funct Genomics*. **2016**;*15*:298-304.
[50] Krintel SB, Palermo G, Johansen JS, et al. Investigation of single nucleotide polymorphisms and biological pathways associated with response to TNFα inhibitors in patients with rheumatoid arthritis. *Pharmacogenet Genomics*. **2012**;*22*:577-589.
[51] Prieto-Pérez R, Cabaleiro T, Daudén E, et al. Genetics of psoriasis and pharmacogenetics of biological drugs. *Autoimmune Dis*. **2013**;*2013*:1-13.
[52] Sutherland A, Power RJ, Rahman P, et al. Pharmacogenetics and pharmacogenomics in psoriasis treatment: current challenges and future prospects. *Expert Opin Drug Metab Toxicol*. **2016**;*12*:923-935.
[53] González-Lara L, Batalla A, Coto E, et al. The TNFRSF1B rs1061622 polymorphism (p. M196R) is associated with biological drug outcome in Psoriasis patients. *Arch Dermatol Res*. **2015**;*307*:405-412.
[54] Julià A, Marsal S. Pharmacogenomics of anti-TNF response in psoriasis, where are we? *Pharmacogenomics*. **2016**;*17*:323-326.
[55] O'Rielly DD, Rahman P. Pharmacogenetics of psoriasis. *Pharmacogenomics*. **2011**;*12*:87-101.
[56] Tsoi LC, Spain SL, Ellinghaus E, et al. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. *Nat Commun*. **2015**;*6*:7001.
[57] Stelzer G, Rosen N, Plaschkes I, et al. The genecards suite: from gene data mining to disease genome sequence analyses. *Curr Protoc Bioinforma*. **2016**;*54*(1):1.30.1-1.30.33.
[58] Aterido A, Palau N, Domènech E, et al. Genetic association between CD96 locus and immunogenicity to anti-TNF therapy in Crohn's disease. *Pharmacogenomics J*. **2019**;*19*:547-555..
[59] Talmont F, Moulédous L, Piedra-Garcia L, et al. Pharmacological characterization of the mouse NPFF2 receptor. *Peptides*. **2010**;*31*:215-220.

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