Polymorphisms associated with adalimumab and infliximab response in moderate-to-severe plaque psoriasis

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Aims-. This study evaluated the influence of pharmacogenetics in psoriatic patients treated with adalimumab and/or infliximab. **Materials and methods-.** Prospective observational study evaluating the association of 124 polymorphisms with the response to adalimumab or infliximab (PASI75) in patients with moderate-to-severe plaque psoriasis at 3 months (N=95) and 6 months of treatment (N=90). Significant SNPs for univariate analysis were subjected to multivariate analysis. **Results/Conclusions-**. Five SNPs were associated with PASI75 at 3 months: rs6661932 (*IVL*), rs2546890 (*IL12B*), rs2145623 (*NFKBIA*), rs9304742 (*ZNF816A*) and rs645544 (*SLC9A8*). Furthermore, rs1061624 (*TNFR1B*) was associated with PASI75 at 6 months. Nevertheless, these biomarkers should be validated in large-scale studies before implementation in clinical practice.

1. Introduction

Psoriasis is a chronic and inflammatory disease that affects 2-3% of the world population [1,2]. Apart from affecting the skin, where it generates scaly erythematous papules and plaques [3], it may course with a wide range of comorbidities such as psoriatic arthritis, inflammatory bowel disease, cardiovascular and psychosocial conditions that impair quality of life [1,4,5]. Although the etiology of psoriasis remains unknown, family and twins studies have demonstrated that genetic factors play an important role in the onset and development of this disease [6–8]. In fact, the presence of the *HLA-C*:06:02* allele [9,10] and polymorphisms in different genes such as tumor necrosis factor α (TNFα), interleukins 12, 17 and 23 (IL-17, IL-12, IL-23), are potential risk factors in psoriasis [11,12]. Approved biologic drugs that target TNF (adalimumab,

etanercept and infliximab) are currently used as first line biological treatment for moderate-to-severe psoriasis resistant to other systemic treatments [13].

Adalimumab and infliximab are both TNF blocking antibodies. While adalimumab is a fully human monoclonal antibody, infliximab is a chimeric mouse monoclonal antibody against TNFα [14,15]. TNFα blocking antibodies are safe and effective drugs for psoriasis [16–18]. Nevertheless, they are expensive and, although rarely, they might cause serious adverse effects [18,19]. Moreover, around 30% of the patients do not respond to these treatments [18,19]. Both molecules share structure and can bind and fix complement. Therefore they can lyse cells that express TNFα on their surface [20]. However, etanercept, a soluble form of p75 TNFα receptor, cannot accomplish that function [14,20]. Structural differences between etanercept and TNFα blocking antibodies may be the cause of the dissimilarities found in the efficacy of the TNFα blocking agents. Thus, the main objective of this paper is to identify pharmacogenetic biomarkers that could identify non-responder patients to TNFα blocking antibodies (adalimumab and infliximab).

2. Material and methods

2.1. Experimental design

This study included 95 patients treated with monoclonal antibodies targeting TNFα from the Dermatology Unit of the Hospital Universitario de La Princesa in Madrid, Spain. When a patient was treated with both antibodies, only the first drug was considered. Inclusion criteria of this study were the following: Caucasian patients older than 18 years that were diagnosed for moderate-to-severe psoriasis according to the Spanish Academy of Dermatology and Venereology Psoriasis Working Group

consensus document criteria [21]. They received adalimumab or infliximab treatment according to the Summary of Product Characteristics. Psoriasis Area and Severity Index (PASI) was used as effectiveness criteria to evaluate TNFα blocking antibodies response at 3 and 6 months of treatment. Patients that reduced at least 75% over their baseline PASI (PASI75) were considered responders to TNFα blocking antibodies. All the subjects included in this study signed a written informed consent that allowed SNPs genotyping. The protocol and informed consent document fulfilled Spanish law on biomedical research and both were 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 peripheral blood was extracted from each patient. DNA extraction was performed using the MagNa Pure® System (Roche Applied Science, USA) and quantified with a NanoDrop® ND-1000 Spectrophotometer (Wilmington, USA). Samples were stored at -80 ºC in the Clinical Pharmacology Department of the Hospital Universitario de La Princesa. We selected 124 polymorphisms based on an extensive review of articles describing the association between polymorphisms and multiple inflammatory diseases related to psoriasis (rheumatoid arthritis, psoriatic arthritis, Crohn's disease) and response to biological drugs [22]. A list of all evaluated SNPs is shown in Supplementary Table 1. Three *IL-17* polymorphisms were evaluated using human TaqMan® SNP Genotyping Assays (StepOne, Applied Biosystems, USA) as described previously [23] while one hundred and twenty one SNPs were evaluated using the Illumina Veracode genotyping platform (Human Genotyping Unit-CeGen, Madrid, Spain) [24].

2.3. Statistical analysis

Linkage disequilibrium, Hardy-Weinberg equilibrium (HWE), allele and genotype frequencies and the association between the SNPs and adalimumab and infliximab response were performed using the SNPStats program (Catalan Institute of Oncology, Barcelona, Spain) [25]. Only the SNPs which allele frequencies were in HWE were included in the multivariate analysis [26]. Every SNP was tested to determine which logistic regression model had the best adjustment according to the type of inheritance (dominant, recessive, codominant or additive). The optimal model was selected using the lower p value and the lower Akaike Information Criterion (AIC) [24]. Results were expressed as the odds ratio (OR), the 95% confidence interval (CI), and the p value. SNPs with $p<0.05$ in the univariate analysis were included in a multivariate logistic regression model using the SPSS programme (IBM SPSS v19 Inc Chicago, IL, USA). Moreover, when several SNPs were in linkage disequilibrium and were significant in the univariate analysis, we analyzed the association between haplotype and response using SNPstats. Statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Study population

Sixty-eight patients were treated with adalimumab: 42 patients as the first biologic treatment option, 21 as the second therapeutic option and 5 as the third option. Thirty-four patients were subjected to treatment with infliximab: 28 patients as the first biologic option, 5 as the second treatment and 1 as the third therapeutic option. When both treatments were administered to the same patient, only the first biologic drug of these two possible options was considered (N=95): 32 with infliximab and 63 with

adalimumab. Seven patients received adalimumab and infliximab: 3 were both responders to infliximab and adalimumab and 4 failed to respond to both. Sixty-seven patients achieved a PASI75 response at 3 months of treatment (70.5%: 64.7% with adalimumab and 73.5% with infliximab). There were no differences between responders and non-responders in the clinical and demographic variables analyzed (Table 1). Ninety patients completed adalimumab or infliximab treatment for 6 months and 72 of these patients achieved a PASI75 (80.0 %: 82.5% with adalimumab and 86.2% with infliximab).

3.2. Effectiveness

There was no association between the response to treatment (PASI75 at 3 months) and the following clinical or demographic characteristics: therapeutic option (p=0.360), gender (p=0.880), weight (p=0.290), age of the first biologic agent (p=0.680), age of onset of psoriasis (p=0.670), type of psoriasis (p=0.660), or presence of psoriatic arthritis (p=0.730).

From the 124 SNPs analyzed, only 9 were not in HWE: rs10494292 (*LELP1*; p=0.037), rs187238 (*IL-18*; p=0.042), rs3812888 (*COG6*; p=0.041), rs11126740 (*CTNNA2*; p=0.047), rs2787094 (*ADAM33*; p=0.022), rs658971 (*SLC12A8*; p=0.037), rs12191877 (*HLA-C*; p=0.034), rs3027898 (*IRAK1;* p<0.001), rs3761548 (*FOXP3*; p<0.001). These SNPs were not included in the analysis.

At 3 months of treatment, univariate analysis showed significant differences in PASI75 for 19 SNPs (Table 2). However, when they were tested for multivariate analysis, significant results were only obtained for five polymorphisms: rs6661932 (*IVL*),

rs2546890 (*IL12B*), rs2145623 (*NFKBIA*), rs9304742 (*ZNF816A*) and rs645544 (*SLC9A8*). Polymorphisms in the *IVL*, *NFκB* and *SLC9A8* genes increased the risk of no response to adalimumab or infliximab whereas SNPs in the *IL-12B* and the *ZNF816A* genes reduced the risk of no response to these biologic drugs.

There was no association of the response to treatment (PASI75 at 6 months) and the following clinical or demographic characteristics: therapeutic option (p=0.520), gender (p=0.830), weight (p=0.920), age of the first biologic agent (p=0.440), age of onset of psoriasis (p=0.210), type of psoriasis (p=0.093), or presence of psoriatic arthritis (p=0.690).

Moreover, we analyzed the association of the 124 SNPs with the response at 6 months in the 90 patients that continued with the treatment of adalimumab or infliximab. Only 8 SNPs were not in HWE: rs2485558 (*RYR2*; p=0.049), rs187238 (*IL-18*; p=0.019), rs10494292 (*LELP1*; p=0.035), rs3812888 (*COG6*; p=0.034), rs2787094 (*ADAM33*; p=0.020), rs658971 (*SLC12A8*; p=0.035), rs3027898 (*IRAK1*; p<0.001), rs3761548 (*FOXP3*; p<0.001). These SNPs were not included in the analysis.

At 6 months of treatment, univariate analysis showed significant differences in PASI75 for 12 SNPs (Table 3). However, when we performed multivariate analysis only one SNP reduced the risk of no response to adalimumab or infliximab: rs1061624 (*TNFR1B*).

4. Discussion

Several pharmacogenetic studies have been performed to detect genetic biomarkers that could predict TNFα blocking antibodies in psoriasis (Table 4) [24,27–40]. Our study is the first to analyze the association of a high number of candidate SNPs (N=124) with TNFα blocking antibodies treatment in psoriasis patients. We have made a comparison of the previous publications that studied SNPs which could affect anti-TNF drug response (Table 4) [24,27–40]. However, only few of these publications have focused on the specific markers that could predict adalimumab and infliximab response. We have found 5 SNPs associated with TNFα blocking antibodies response. The SNPs are the following: rs6661932 (*IVL*), rs2546890 (*IL-12B*), rs2145623 (*NFKBIA*), rs9304742 (*ZNF816A*) and rs645544 (*SLC9A8*), were associated with PASI75 at 3 months. Furthermore, rs1061624 (*TNFR1B*) was associated with PASI75 at 6 months.

IVL is a product of the *PSORS4* locus, located on chromosome 1q21 in the epidermal differentiation complex region and widely associated with psoriasis susceptibility that encodes involucrin [41]. Involucrin is a protein involved in keratinocytes and epidermal differentiation that plays an important role in psoriasis [42]. rs6661932 (*IVL*) has been associated with early onset of psoriasis in a Chinese population [43]. However, it has not been previously associated with anti-TNF drug response. Our study shows that carriers of the T allele of rs6661932 (*IVL*) were less likely to respond to infliximab or adalimumab.

IL-12B is a proinflammatory cytokine that induces T helper 1 (Th1) pathway. Previous publications have suggested that IL-12B plays an important role in psoriasis

development [12,44,45]. Furthermore, rs2546890 (*IL-12B*) is associated with the susceptibility to develop psoriasis [46] and to develop psoriatic arthritis in psoriasis patients [47]. Although the polymorphisms in *IL-12B* (rs6887695 and rs3212227) do not influence the response globally to anti-TNF drugs [28], we found that carriers of the A allele in rs2546890 are more likely to respond to adalimumab or infliximab. These results agree with a previous publication from our laboratory that demonstrated that carriers of the G allele in this polymorphisms were more likely not to respond globally to anti-TNF drugs [24].

Furthermore, *NFKBIA* encodes a member of the NF-κB inhibitor family; a negative inhibitor of the immune response that plays an important role in psoriasis [48]. rs2145623 (*NFKBIA*) was associated with psoriasis susceptibility in a previous publication [46]. We have shown that carriers of the G allele in this SNP are less likely to respond to infliximab or adalimumab. This SNP has previously been associated with ustekinumab (a different drug used to treat moderate-to-severe psoriasis) response [49]. Nevertheless, previous publications failed to find an association between rs2145623 (*NFKBIA*) and etanercept response [50,51].

ZNF816A gene encodes a zinc-finger transcription factor involved in different regulatory functions such as the recognition of RNA and proteins [52]. rs9304742 (*ZNF816A*) has previously been associated with psoriasis susceptibility [8,53]. Our results showed that the presence of the C allele of this SNP is associated with a better response to TNFα blocking antibodies. However, a previous publication from our laboratory has demonstrated that carriers of the C allele for rs9304742 (*ZNF816A*) were less prone to respond globally to TNFα blockers (adalimumab, etanercept and

infliximab) [24]. Nevertheless, further studies with a higher number of patients should be done to confirm these results. Carriers of the C allele for rs9304742 (*ZNF816A*) were more likely to respond to ustekinumab in psoriasis patients [49].

SLC9A8 encodes a sodium-hydrogen exchanger which is in the group of integral transmembrane proteins that exchange extracellular Na^+ for intracellular H^+ [54]. These channels have multiple functions, which include regulation of cell volume, intracellular pH homeostasis and electroneutral NaCl absorption in epithelia [54]. rs645544 (*SLC9A8*) has been previously associated with psoriasis susceptibility [55]. Nevertheless, it has not been associated with anti-TNF drugs´ response so far. The present study shows that carriers of the G allele for the rs645544 SNP are less likely to respond to TNFα blocking antibodies.

TNFR1B encodes the receptor of tumor necrosis factor. Polymorphisms in this gene have been previously associated with psoriasis susceptibility [56]. Our results show that carriers of the G allele in rs1061624 (*TNFR1B*) have more probability to respond to infliximab or adalimumab at 6 months. Although *TNFR1B* rs1061624 and rs3397 did not independently associate with infliximab efficacy, the AT haplotype (rs1061624A – rs3397 T) had a significant difference in distribution in responders and non-responders to infliximab in Crohn´s disease [56]. To our knowledge, no publications have analyzed the prediction value of the AT haplotype in adalimumab response. Moreover, the GT haplotype (rs2230926 T – rs610604 G) was associated with a good response to all TNFα blocking agents [37]. Two studies have shown that carriers of the G allele for the

rs1061622 (*TNFR1B*) SNP were more likely not to respond globally to anti-TNF drugs [32,57].

Table 4 summarizes previous pharmacogenetic studies that searched for biomarkers which could predict anti-TNF drugs response in psoriasis. From the 21 SNPs that have been previously associated to anti-TNF drugs response, we have analyzed 10 in the present paper. We have only confirmed one of them [rs2546890 (*IL12B*)] in the multivariate analysis. However, five more SNPs [rs1801274 (*FCGR2A*), rs6311 (*HTR2A*), rs96844 (*MAP3K1*), rs1061622 (*TNFRSF1B*) and rs2230926/rs610604 (*TNFAIP3*)] were confirmed in the univariate analysis but not in the multivariate analysis. These discrepancies may be explained by the diverse SNPs and covariates included in the analysis. Our study analyzes simultaneously 124 SNPs while most of the pharmacogenetic studies focus on a maximum of 6 SNPs. Thus, these results may be influenced by the diverse number of SNPs and factors included in the multivariate analysis of the different publications. Besides, we have to consider that most of the previous studies have been performed in patients treated with any of the approved anti-TNF agents (adalimumab, etanercept and infliximab) whereas this present publication focuses in the response to adalimumab or infliximab.

A previous study showed that patients presenting the C allele in rs763780 (*IL-17F*) were more likely not to respond to infliximab [23]. However, no differences were observed between responders and non-responders to adalimumab and infliximab in the present publication. These results suggest that rs763780 (*IL-17F*) may be a specific marker of infliximab response. Furthermore, a previous publication showed that patients carrying the A allele in the rs11209026 (*IL-23R*) polymorphism were more likely not to respond

to a 6 months treatment with infliximab [28]. However, this result was not confirmed in the present study that analyzed simultaneously adalimumab and infliximab response. Therefore, these results suggest that rs11209026 (*IL-23R*) may be a specific biomarker of infliximab response at 6 months of treatment.

In the present study we show that rs12191877 (*HLA-C*) is not associated with adalimumab response. This SNP has also been associated with psoriasis and is in linkage disequilibrium with *HLA-C*0602* [58,59]. These results agree with those of a recent article published by Talamonti *et al.* 2017 [60]. They showed that the presence of the *HLA-C:06:02* allele could not predict long –term adalimumab response in moderate-to-severe Italian patients (n=122). Taken together, these two studies suggest that the presence of the *HLA-C*0602* allele cannot predict short- term nor long-term response to adalimumab.

The main limitation of this study is the small sample size. Nevertheless, this is an observational study that does not interfere with routine clinical practice so the study population was limited by the number of patients subjected to treatment with adalimumab or infliximab. This reduced sample size [adalimumab (N=68) and infliximab (N=34)] did not allow us to perform an individual analysis with any of these drugs. Nevertheless, the reduced sample size was compensated by an exhaustive follow-up of patients and a deep analysis of their data. Few studies have evaluated the effect of polymorphisms on the response to TNFα blocking antibodies in moderate-to-severe psoriasis [24,27–33]. Consequently, our findings are an addition to current knowledge on the pharmacogenetics of moderate-to-severe plaque psoriasis. This type of studies could help optimizing the effectiveness of psoriasis therapy, thereby increasing its cost-

effectiveness and decreasing the risk of adverse events. Nevertheless, further studies would be necessary to implement these genetic tests to the clinical practice.

5. Conclusions

A few studies have been performed about the pharmacogenetics of adalimumab and infliximab treatment in psoriatic patients. Polymorphisms in *IVL, IL-12B, NFKBIA, ZNF816A* and *SLC9A8* genes were associated with PASI75 at 3 months of adalimumab or infliximab treatment. Moreover, a SNP located in *TNFR1B* was associated with PASI75 at 6 months of treatment with adalimumab or infliximab.

6. Executive summary

Background

- Adalimumab and infliximab are antibodies against TNFα. Although they are effective drugs to treat moderate-to-severe psoriasis, not all patients get an adequate response and some patients may develop adverse effects. A few studies have evaluated the influence of pharmacogenetic in patients with psoriasis treated with anti-TNF agents (Table 1).

Patients & methods

- We evaluated the association between 124 polymorphisms and the response to adalimumab or infliximab (PASI75) at 3 and 6 months of treatment in 95 and 90 patients respectively. We tested different logistic regression models and adjusted our results using multivariate analysis.

Results & conclusion

- We found an association between SNPs in *IL-12B*, *IVL, SLC9A8*, *NFKBIA*, *ZNF816A* genes and adalimumab or infliximab response at 3 months of treatment.
- We found that a SNP in *TNFR1B* could predict adalimumab or infliximab response at 6 months of treatment.
- Further studies would be necessary to confirm the role of these genes in the response to adalimumab and infliximab.

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Table 1. Phenotypic characteristics of psoriatic patients treated with adalimumab and infliximab.

	Patients (N=95)	**Responders (N=67)**	**Non-responders (N=28)**	**Statistical significance**
Age at onset of psoriasis (years)	27.8± 12.8	27.5 ± 13.1	28.7 ± 12.2	p=0.400
Men (%)	60 (63.2)	42 (62.7)	18 (64.3)	p=0.833
Weight (Kg)	76.4 ± 13.3	75.5 ± 13.3	78.7± 13.1	p=0.972
Adalimumab (%)	63 (66.3)	43 (64.2)	20 (71.4)	p=0.495
Infliximab (%)	32 (33.7)	24 (35.8)	8 (28.6)	
Psoriasis Type I (%)[1]	79 (83.2)	55 (82.1)	24 (85.7)	p=0.667
Psoriasis Type II (%)[2]	16 (16.8)	12 (17.9)	4 (14.3)	
Patients with PsA (%)	19 (20.0)	14 (20.9)	5 (17.9)	p=0.736
Age at first biological agent (years)	42.8 ± 14.2	42.4 ± 14.8	43.7± 12.8	p=0.513
Baseline PASI	22.1 ± 11.6	22.6 ± 11.9	20.8 ± 11.0	p=0.529
Clinical response at 3 months of treatment				
PASI at 3 months	3.9 ± 5.6	1.2 ± 1.7	10.3 ± 6.3	p=0.000
PASI75 (%)	67 (70.5)	67 (100)	0 (0)	

Abbreviations: Data are shown as mean and standard deviation or number (%); PsA: psoriatic arthritis; PASI: psoriasis area severity index; [1]early-onset psoriasis (<40 years); [2] late-onset (>40 years); Statistical differences were performed between responders and non-responder patients. T-test and χ^2 were performed for continuous and categorical variables respectively.

Table 2. Summary of the results of univariate and multivariate logistic regression analyses for PASI75 at 3 months of treatment (N=95). Only polymorphisms significant for the univariate analysis ($p<0.05$) are shown and were included in the multivariate analysis.

				UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
SNP	**Gene**	**Model**	**Risk Genotype (% Responders /% Non-responders)**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
rs1800896	*IL-10*	A	AG-GG (64.2-81.5)	2.19 (1.07-4.47)	0.028	2.46 (0.53-11.37)	0.249
rs2243188	*IL-19*	R	AA (10.4-0.0)	0.00 (0.00-ND)	0.024	0.00 (0.00-ND)	0.999
rs6661932	***IVL***	**A**	**CT-TT (65.7-85.2)**	**2.15 (1.09-4.21)**	**0.022**	**13.08 (1.11-154.37)**	**0.041**
rs821421	*PGLYRP3*	D	AC-AA (23.9-53.6)	3.68 (1.45-9.33)	0.006	3.17 (0.33-30.86)	0.321
rs1500941	*SPRR2F*	D	AG-GG (74.6-53.6)	0.39 (0.16-0.99)	0.048	0.41 (0.02-8.94)	0.567
rs191190	*TNFR1*	C	CT (46.3-75.0)	2.71 (0.88-8.35)	0.024	0.02 (0.00-4.31)	0.148
rs7744	*MyD88*	A	AG-GG (16.4-35.7)	2.49 (1.07-5.82)	0.003	0.72 (0.06-8.47)	0.796
rs2546890	***IL-12B***	**A**	**AG-AA (80.6-60.7)**	**0.42 (0.20-0.87)**	**0.015**	**0.12 (0.01-0.95)**	**0.044**
rs2431697	*PTTG1*	R	CC (13.4-33.3)	3.22 (1.11-9.34)	0.032	10.85 (0.69-171.36)	0.090
rs1050152	*SLC22A4*	A	CT-TT (74.6-57.1)	0.51(0.28-0.95)	0.028	0.47 (0.09-2.45)	0.366
rs6908425	*CDKAL1*	A	CT-TT (34.3-17.9)	0.41 (0.15-1.09)	0.050	0.64 (0.00-1.12)	0.060
rs610604	*TNFAIP3*	R	CC (19.4-3.6)	0.15 (0.02-1.24)	0.027	0.02 (0.00-5.97)	0.173
rs774359	*C9orf72*	R	CC (9.1-0.0)	0.00 (0.00-ND)	0.038	0.00 (0.00-ND)	0.999
rs2145623	***NFKBIA***	**A**	**CG-GG (50.0-67.9)**	**1.98 (1.04-3.75)**	**0.034**	**6.64 (1.13-39.23)**	**0.037**
rs4775912	*USP8-TNFAIP8L3*	A	CT-CC (34.3-14.3)	0.33 (0.11-0.99)	0.027	0.09 (0.00-1.45)	0.089
rs4792847	*MAP3K14*	D	AG-AA (57.6-78.6)	2.70 (0.97-7.54)	0.047	5.09 (0.35-73.35)	0.232
rs4788850	*NAT9*	D	CG (11.9-0.0)	0.00 (0.00-ND)	0.015	0.00 (0.00-ND)	0.999
rs9304742	***ZNF816A***	**D**	**CT-CC (70.2-42.9)**	**0.32 (0.13-0.80)**	**0.013**	**0.01 (0.00-0.30)**	**0.008**
rs645544	***SLC9A8***	**R**	**GG (6.0-21.4)**	**4.30 (1.11-16.65)**	**0.033**	**73.54 (1.33-4,075.18)**	**0.036**

Abbreviations: *IL-10*: Interleukin 10; *IL-19*: Interleukin 19; *IVL*: Involucrin; *PGLYRP3;* Peptidoglycan Recognition Protein 3; *SPRR2F:* Small Proline Rich Protein 2F; *TNFR1*: Tumor Necrosis Factor Receptor 1; *MyD88*: Myeloid Differentiation Primary Response 88; *IL12B*: Interleukin 12B; *PTTG1*: Pituitary Tumor-Transforming 1; *SLC22A4:* Soluble Carrier Family 22 member 4; *CDKAL1:* CDK5 Regulatory Subunit Associated Protein 1 Like 1; *TNFAIP3*: TNF Alpha Induced Protein 3; *C9orf72*: Chromosome 9 open reading frame 72; *NFKBIA:* NFκB Inhibitor Alpha; *USP8-TNFAIP8L3*: Ubiquitin Specific Peptidase 8 - TNFα Alpha Induced Protein 8 Like 3; *MAP3K14:* Mitogen-Activated Protein Kinase Kinase Kinase 14*; NAT9*: N-acetyltransferase 9*; ZNF816A*: Zinc Finger Protein 816; *SLC9A8*: Soluble Carrier Family 9 member A8; SNP: Single Nucleotide Polymorphism; OR: Odds Ratio of non-response; CI: Confidence Interval; C: Codominant; D: Dominant; A: Additive; R: Recessive; ND: No Data. Bold characters emphasize significant results for multivariate analysis.

Table 3. Results of univariate and multivariate logistic regression analyses for PASI75 at 6 months of treatment (N=90). Only polymorphisms significant for the univariate analysis ($p<0.05$) are shown and were included in the multivariate analysis.

				UNIVARIATE ANALYSIS		**MULTIVARIATE ANALYSIS**	
SNP	**Gene**	**Model**	**Risk Genotype (% Responders/ % Non-responders)**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
rs1800896	*IL-10*	A	AC-AA(49.3- 27.8)	0.39 (0.14-1.08)	0.048	0.69 (0.26-1.85)	0.457
rs1500941	*SPRR2F*	D	AG-GG (75.0-50.0)	0.33 (0.11-0.97)	0.045	0.43 (0.12-1.54)	0.194
rs1061622	*TNFR1B*	D	GT-GG (34.7-66.7)	3.76 (1.26-11.22)	0.014	2.01 (0.56-7.21)	0.286
rs1061624	***TNFR1B***	**A**	**AG-GG (73.5-93.3)**	**2.94 (1.15-7.53)**	**0.018**	**0.32 (0.12-0.86)**	**0.025**
rs397211	*IL-1RN*	R	CC (15.5-0.0)	0.00 (0.00-ND)	0.021	2.04 (0.36-11.5)	0.419
rs96844	*MAP3K1*	D	CT-CC (52.8-16.7)	0.18 (0.05-0.67)	0.004	0.40 (0.11-1.37)	0.143
rs2431697	*PTTG1*	A	CT-CC (63.4-83.3)	2.53 (1.15-5.54)	0.016	2.00 (0.85-4.74)	0.115
rs13437088	*HLA-B/MICA*	R	TT (13.9-0)	0.00 (0.00-ND)	0.029	0.92 (0.13-6.71)	0.930
rs2395029	*HPC5*	D	GT (12.5-0)	0.00 (0.00-ND)	0.039	0.50 (0.03-8.34)	0.630
rs6311	*5-HTR2A*	D	CC -CT (67.6-93.8)	7.19 (0.89-57.76)	0.018	0.62 (0.16-2.38)	0.485
rs12459358	*PSORS6*	D	CT-TT (64.8-33.3)	0.27 (0.09-0.81)	0.016	1.52 (0.45-5.16)	0.503

Abbreviations: *IL-10*: Interleukin 10; *SPRR2F*: Small Proline Rich Protein 2F; *TNFR1B*: Tumor Necrosis Factor Receptor 1B; *IL-1RN*: Interleukin 1 Receptor Antagonist; *MAP3K1:* Mitogen-Activated Protein Kinase Kinase Kinase 1; *PTTG1*: Pituitary Tumor-Transforming 1*; HLA-B/MICA*: Human Leukocyte Antigen B/Mayor Histocompatibility Complex Class I Polypeptide-Related Sequence A; *HLA-B/MICA*: *HPC5:* HLA Complex P5*; 5-HTR2A:* 5 Hydroxytryptamine Receptors 2A; *PSOR6:* Psoriasis 6; SNP: Single Nucleotide Polymorphism; OR: Odds Ratio of non-response; CI: Confidence Interval; D: Dominant; A: Additive; R: Recessive; ND: No Data. Bold characters represent significant results.

Table 4. SNPs associated with response to biological therapies in psoriasis patients in previous studies and correlation with the present study. Only significant results p<0.05 appear in this table.

Gene	SNP	RG	N	Drugs	Period	Response Criteria	Reference	C
CTNNA2	rs11126740	AA	144	Anti-TNF	3	PASI75	Prieto-Pérez et al. [24]	NA
FCGR2A	rs1801274	T	144	Anti-TNF	6	PASI75	Prieto-Pérez et al. [24]	CU
HLA-C	rs12191877	C	144	Anti-TNF	3	PASI75	Prieto-Pérez et al. [24]	NC
HTR2A	rs6311	T	144	Anti-TNF	6	PASI75	Prieto-Pérez et al. [24]	CU
IL-12B	rs2546890	A	144	Anti-TNF	3&6&12	PASI75	Prieto-Pérez et al. [24]	C
IL-17A	rs4819554	AA	205	Anti-TNF	3	PASI75	Batalla et al. [27]	NA
IL-17F	rs763780	TT	35/ 62	IFX/ ADA	3&6/ 6	PASI75	Prieto-Pérez et al. [23]	NC
IL-23R	rs11209026	GG	33	IFX	6	PASI90	Gallo et al. [28]	NC
MAP3K1	rs96844	T	144	Anti-TNF	3&6	PASI75	Prieto-Pérez et al. [24]	CU
TNFα (-238)	rs361525	G	109/27 270 57/ 270/ 80	Anti-TNF/IFX Anti-TNF	6 3/ 2	PASI75/ %ImPASI/ PASI75	Gallo et al. [28]/ Murdaca et al. [61]/ Song et al. [39]/ Vasilopoulos et al.[32]	NA
TNFα (-308)	rs1800629	G	270	Anti-TNF		PASI75	Song et al.[39]	NA
TNFα (-857)	rs1799724	CC	109/ 27/ 80/ 270	Anti-TNF/ IFX Anti-TNF	6	%ImPASI / PASI50&PASI75 PASI75	Gallo et al. [28]/ Vasilopoulos et al.[32]/ Song et al. [39]	NA
TNFα (-1031)	rs1799964	TT	109/27	Anti-TNF / IFX	3&6	PASI75/ PASI50 & PASI75& PASI90	Gallo et al. [28]	NA
TNFRSF1B	rs1061622	TT	80/ 90	Anti-TNF	6	PASI75 / PASI50	Vasilopoulos et al. [32]/González-Lara et al. [57]	CU
TNFAIP3	rs2230926 /rs610604	A	250	ADA	6	PASI75	Masouri et al. [42]	CU
	rs2230926 /rs610604	T	55	Anti-TNF		PASI50	Chen et al. [40]	
	rs2230926 /rs610604	GG	433/51	Anti-TNF	3/ 6	PASI50	Talamonti et al. [62]/ Tejasvi et al. [37]	
	rs2230926/ rs610604	TG	433	Anti-TNF	6	PASI50	Tejasvi et al. [37]	
	rs2230926/ rs610604	TG	632	Anti-TNF	6	PASI50	Tejasvi et al. [37]	
	rs2230926	TG	51	Anti-TNF	3	PASI75	Talamonti et al.[62]	
PDE3A- SLCO1C1	rs379471	G	103	Anti-TNF	3	%ImPASI	Julià et al. [30]	NA
	rs1048554	C	250	Anti-TNF	6	PASI75	Masouri et al. [35]	
	rs9260313	TT	250	ADA	6	PASI75	Masouri et al. [35]	
PGLYRP4-24	rs2916205	AA	144	Anti-TNF	3	PASI75	Prieto-Pérez et al. [24]	NA
TRAF3IP2	rs13190932	GG	250	IFX	6	PASI75	Masouri et al. [35]	NA
ZNF816A	rs9304742	T	144	Anti-TNF	3	PASI75	Prieto-Pérez et al. [24]	NC

Abbreviations: RG: Allele or genotype of response. N: number of patients; C: Confirmation of the genetic biomarkers in the present study; NA: not analyzed; NC: not confirmed in our study population; CU: Confirmed only in the univariate analysis; PASI: Psoriasis Area and Severity Index; PASI50: 50% of improvement respect basal PASI; PASI75: 75% of improvement respect basal PASI; PASI90: 90% of improvement respect basal PASI; ImPASI: Improvement of PASI; Anti- TNF: Anti- Tumor Necrosis Factor; ADA: Adalimumab; IFX: Infliximab.

Supplementary Table 1. Information of the 124 SNPs studied in the present study.

Nº	SNP	CHROMOSOME	REGION	GENE	MINOR ALLELE	AMINOACID CHANGE
1	**rs699**	1	Coding	*AGT*	C	Pro>Leu
2	**rs928655**	1	Intronic	*GBP6*	G	No
3	**rs1800896**	1	Intergenic	*IL10*	G	No
4	**rs1800872**	1	Intergenic	*IL10*	G	No
5	**rs2243188**	1	Intronic	*IL19*	A	No
6	**rs2243158**	1	Intronic	*IL19*	C	No
7	**rs11209026**	1	Coding	*IL23R*	A	Lys>Glu
8	**rs4649203**	1	Intergenic	*IL28RA*	G	No
9	**rs6661932**	1	Intergenic	*IVL*	T	No
10	**rs6701216**	1	Intronic	*LCE*	T	No
11	**rs1886734**	1	Intronic	*LCE*	A	No
12	**rs4112788**	1	Intergenic	*LCE*	T	No
13	**rs983332**	1	Intergenic	*LMO4*	A	No
14	**rs10494292**	1	Intergenic	*LELP1*	G	No
15	**rs6684865**	1	Intronic	*MMEL-TNFRSF14*	A	No
16	**rs1801133**	1	Coding	*MTHFR*	T	Ala>Val
17	**rs10754555**	1	Intronic	*NLRP3*	G	No
18	**rs2240340**	1	Intronic	*PADI4*	A	No
19	**rs821421**	1	Intergenic	*PGLYRP3-19*	A	No
20	**rs2206593**	1	UTR	*PTGS2*	A	No
21	**rs2476601**	1	Coding	*PTPN22*	A	Arg>Trp
22	**rs10919563**	1	Intronic	*PTPRC*	A	No
23	**rs2485558**	1	Intronic	*RYR2*	G	No
24	**rs1500941**	1	Intergenic	*SPRR2F*	G	No
25	**rs191190**	1	Intronic	*TNFR1*	C	No
26	**rs1061622**	1	Coding	*TNFR1B*	G	Gly>Trp
27	**rs1061624**	1	UTR	*TNFR1B*	A	No
28	**rs3087243**	2	Intergenic	*CTLA4*	G	No
29	**rs11126740**	2	Intronic	*CTNNA2*	A	No
30	**rs842636**	2	Intergenic	*LINC01185*	A	No
31	**rs2164807**	2	Intergenic	*GNLY-ATOH8*	G	No
32	**rs17716942**	2	Intronic	*IFIH1*	C	No
33	**rs17561**	2	Coding	*IL1A*	T	Val>Leu
34	**rs397211**	2	Intergenic	*IL1RN*	C	No
35	**rs13393173**	2	Intronic	*LASS6*	A	No

Nº	SNP	CHROMOSOME	REGION	GENE	MINOR ALLELE	AMINOACID CHANGE
36	**rs7574865**	2	Intronic	*STAT4*	T	No
37	**rs7744**	3	UTR	*MyD88*	G	No
38	**rs1801282**	3	Coding	*PPAR-γ*	G	Pro>Ala
39	**rs658971**	3	Intronic	*SLC12A8*	A	No
40	**rs651630**	3	Intronic	*SLC12A8*	T	No
41	**rs437943**	4	Intergenic	*EPS15*	G	No
42	**rs6822844**	4	Intergenic	*IL21*	T	No
43	**rs11096957**	4	Coding	*TLR10/1/6*	C	Tyr>Ser
44	**rs2289318**	4	Intronic	*TLR2*	G	No
45	**rs1232027**	5	Intergenic	*DHFR*	A	No
46	**rs3213094**	5	Intronic	*IL12B*	A	No
47	**rs2546890**	5	Intergenic	*IL12B*	A	No
48	**rs1800925**	5	Intergenic	*IL13*	T	No
49	**rs848**	5	UTR	*IL13*	T	No
50	**rs96844**	5	Intergenic	*MAP3K1*	C	No
51	**rs2431697**	5	Intergenic	*PTTG1*	C	No
52	**rs1050152**	5	Coding	*SLC22A4*	T	No
53	**rs17728338**	5	Intergenic	*TNIP1*	A	No
54	**rs2073048**	6	Intronic	*C6orf10*	T	No
55	**rs879882**	6	Intergenic	*HLA-C*	T	No
56	**rs13437088**	6	Intergenic	*HLA-B/MICA*	T	No
57	**rs12191877**	6	Intergenic	*HLA-C*	T	No
58	**rs2395029**	6	Coding	*HPC5*	G	Gly>Trp
59	**rs2275913**	6	Intronic	*IL17A*	C	His>Arg
60	**rs10484879**	6	Intronic	*IL17A*	A	No
61	**rs763780**	6	Intergenic	*IL17F*	T	No
62	**rs1342642**	6	Coding	*IL20RA*	T	Thr>Ile
63	**rs1167846**	6	Intronic	*IL20RA*	T	No
64	**rs2010963**	6	UTR	*VEGF*	C	No
65	**rs241447**	6	Coding	*TAP2*	G	Asp>Gly
66	**rs17587**	6	Coding	*LMP*	A	Thr>Ala
67	**rs6920220**	6	Intergenic	*TNFAIP3*	A	No
68	**rs610604**	6	Intronic	*TNFAIP3*	C	No
69	**rs909253**	6	Intronic	*LTA*	C	No
70	**rs240993**	6	Intronic	*TRAF3IP2*	T	No
71	**rs33980500**	6	Coding	*TRAF3IP2*	T	Gln>Stop
72	**rs13210247**	6	Intronic	*TRAF3IP2*	G	No
73	**rs6908425**	6	Intronic	*CDKAL1*	T	No
74	**rs916514**	7	Intronic	*DPP6*	C	No
75	**rs1799983**	7	Coding	*eNOS*	T	Ser>Ile

Nº	SNP	CHROMOSOME	REGION	GENE	MINOR ALLELE	AMINOACID CHANGE
76	**rs1800795**	7	Intergenic	*IL6*	C	No
77	**rs854548**	7	Intergenic	*PON1*	A	No
78	**rs10088247**	8	Intronic	*CSMD1*	C	No
79	**rs11986055**	8	Intronic	*IKBKB*	C	No
80	**rs1799929**	8	Coding	*NAT2*	T	No
81	**rs774359**	9	UTR	*C9orf72*	C	No
82	**rs1076160**	9	Intronic	*TSC1*	A	No
83	**rs4962153**	9	Intronic	*TTP*	A	No
84	**rs11591741**	10	Intronic	*CHUK*	C	No
85	**rs187238**	11	Intergenic	*IL18*	C	No
86	**rs2430561**	12	Intronic	*IFN-γ*	A	No
87	**rs11541076**	12	UTR	*IRAK3*	A	No
88	**rs12580100**	12	Intergenic	*RPS26*	G	No
89	**rs767455**	12	Coding	*TNFR1*	C	No
90	**rs4516035**	12	Intergenic	*VDR*	C	No
91	**rs6311**	13	Intergenic	*5-HTR2A*	T	No
92	**rs3812888**	13	Intronic	*COG6*	C	No
93	**rs7993214**	13	Intronic	*COG6*	T	No
94	**rs3751385**	13	UTR	*GJB2*	T	No
95	**rs2282276**	14	Intronic	*CLMN*	C	No
96	**rs2145623**	14	Intergenic	*NFKBIA*	C	No
97	**rs2254441**	15	Intronic	*PSTP1P1*	A	No
98	**rs4775912**	15	Intronic	*USP8-TNFAIP8L3*	C	No
99	**rs4785452**	16	Intergenic	*CYLD*	T	No
100	**rs10782001**	16	Intronic	*FBXL19*	G	No
101	**rs8056611**	16	Intergenic	*CYLD*	A	No
102	**rs1975974**	17	Intergenic	*C17orf51*	G	No
103	**rs1634517**	17	Intronic	*CCL4L*	A	No
104	**rs4792847**	17	Intronic	*MAP3K14*	A	No
105	**rs1024611**	17	Intergenic	*MCP1*	C	No
106	**rs4788850**	17	Coding	*NAT9*	G	Ala>Gly
107	**rs4795067**	17	Intronic	*NOS2*	G	No
108	**rs763361**	18	Coding	*CD226*	T	Pro>Leu
109	**rs514315**	18	Intergenic	*SERPINB8*	C	No
110	**rs3136645**	19	Coding	*NFKBIB*	C	No
111	**rs9403**	19	UTR	*NFKBIB*	C	No
112	**rs12459358**	19	Intergenic	*PSORS6*	T	No
113	**rs12983316**	19	Intronic	*SMARCA4*	G	No
114	**rs12720356**	19	Coding	*TYK2*	G	Gly>Val
115	**rs9304742**	19	Intergenic	*ZNF816A*	C	No

Nº	SNP	CHROMOSOME	REGION	GENE	MINOR ALLELE	AMINOACID CHANGE
116	**rs597980**	20	Intronic	*ADAM33*	T	No
117	**rs2787094**	20	UTR	*ADAM33*	C	No
118	**rs6138150**	20	Intergenic	*CST5*	C	No
119	**rs6071980**	20	Intergenic	*MAFB*	C	No
120	**rs2769982**	20	Coding	*RNF114*	C	No
121	**rs1008953**	20	Intergenic	*SDC4*	A	No
122	**rs645544**	20	Intronic	*SLC9A8*	G	No
123	**rs3761548**	X	Intronic	*FOXP3*	C	No
124	**rs3027898**	X	Intergenic	*IRAK1*	C	No