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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

Martina Morelli[1,2*], Marco Galluzzo[3*], Stefania Madonna[1], Claudia Scarponi[1], Giovanni Luca Scaglione[1], Tiziana Galluccio[4], Marco Andreani[4], Sabatino Pallotta[1], Giampiero Girolomoni[2], Luca Bianchi[5], Marina Talamonti[5†], and Cristina Albanesi[1†]

[1] IDI-IRCCS, Rome, Italy;
[2] Section of Dermatology, Department of Medicine, University of Verona, Verona, Italy;
[3] Department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy;
[4] Laboratory of Immunogenetics and Transplant, Department of Oncohematology and Cell and Gene Therapy, IRCCS Bambin Gesù Pediatric Hospital, Rome, Italy.
[5] Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy.
* These authors contributed equally to this work
† These authors contributed equally to this work as co-senior authors

ORCIDs:

Martina Morelli: 0000-0001-7299-2393
Marco Galluzzo: 0000-0002-3424-5175
Stefania Madonna: 0000-0003-0585-6783
Claudia Scarponi: 0000-0002-2323-8519
Giovanni Luca Scaglione: 0000-0001-5622-7843
Tiziana Galluccio: 0000-0003-4989-2081
Marco Andreani: 0000-0003-3451-3624
Sabatino Pallotta: 0000-0003-4827-2892
Giampiero Girolomoni: 0000-0001-8548-0493
Luca Bianchi: 0000-0001-8697-6896
Marina Talamonti: 0000-0002-3070-4071
Cristina Albanesi: 0000-0002-7537-6833

Corresponding Author:
Dr. Cristina Albanesi

Laboratory of Experimental Immunology, Istituto Dermopatico dell'Immacolata (IDI)-IRCCS
Via dei Monti di Creta 104, 00167, Rome, Italy
Tel: +39-06-66464776
e-mail: c.albanesi@idi.it

Short Title:
Pharmacogenomics of secukinumab in psoriasis

Abbreviations:
PASI: Psoriasis Area and Severity Index
SNP: Single-Nucleotide Polymorphism
Rs: Reference SNP
PASI75: 75% reduction in Psoriasis Area and Severity Index
PASI90: 90% reduction in Psoriasis Area and Severity Index
PASI100: 100% reduction in Psoriasis Area and Severity Index
NGS: Next-Generation Sequencing
OR: Odds Ratio
CAP: Canonical Analysis of Principal coordinates
BMI: Body Mass Index
LD: Linkage Disequilibrium

ABSTRACT

Objective: Our pharmacogenomic study evaluated the influence of the presence/absence of genetic variants of psoriasis-risk loci on the clinical response to secukinumab. Differences in the single-nucleotide polymorphism (SNP) pattern characterizing HLA-Cw6^{+} or HLA-Cw6^{-} patient subpopulations, showing high or low responses to secukinumab, were also analysed.

Methods: 417 SNPs were analyzed by Next-Generation Sequencing technology, in a cohort of 62 psoriatic patients and undergone secukinumab treatment.

Univariate regression analysis was employed to examine the association between SNP and clinical response to secukinumab. Multivariate analysis was also performed to assess multivariate differences in SNP pattern of HLA-Cw6^{+} or HLA-Cw6^{-} patients showing high or low responses to secukinumab.

Results: Eight SNPs in *HLA-C* and upstream region (rs13207315, rs6900444, rs12189871, rs12191877, rs4406273, and rs10484554), including *HLA-Cw6* classical allele (rs1131118), and three in *MICB-DT* (rs9267325), *DDX58* (rs34085293) and *TYK2* (rs2304255) genes, associating with excellent response to secukinumab were identified. Importantly, rs34085293 or *r*s2304255 SNP status defined a subgroup of super-responder patients. We also found that HLA-Cw6^{+} and HLA-Cw6^{-} patients carried out specific patterns of SNPs associating with different responses to secukinumab.

Conclusion: Assessment of *HLA-Cw6*, together with other allelic variants of genes, could be helpful to define patients which better benefit from anti-IL-17 therapy.

Key words: Psoriasis, SNPs, HLA-Cw6, anti-IL-17A, secukinumab, pharmacogenomics.

1. INTRODUCTION

Psoriasis is an immune-mediated skin disorder caused by inherited susceptibility alleles[1]. Most psoriasis susceptibility loci are related to inflammatory and immune genes. Current opinion on the pathogenesis of psoriasis emphasizes the role of cytokine signaling to drive an inflammatory cycle, in which infiltrating dendritic cells, by releasing IL-23, induce the expansion of autoreactive T lymphocytes, typically represented IL-17-producing T cells[2]. Following their expansion, T cells, together with innate lymphoid cells, γδ-T cells, mast cells and neutrophils release very high amounts of IL-17[3, 4]. IL-17, in turn, mediates most of the epidermal hyperplasia by impairing differentiation of keratinocytes, and inducing their maturation and aberrant cornification. IL-17 also promotes the release of neutrophil- and T-cell-recruiting chemokines and antimicrobial peptides, and synergizes with the pro-inflammatory cytokines IFN-γ and TNF-α[5].

The pathogenic role of IL-17 in psoriasis has been definitely confirmed by the clinical efficacy of secukinumab, the first monoclonal antibody approved for the treatment of psoriasis and targeting IL-17A[6]. Although secukinumab is highly effective[7], variable therapeutic responses have been observed in the psoriatic population, especially in a real-life setting[8].

Biological therapies for psoriasis show significant variability in efficacy in patients, and among factors determining this variability, the presence and/or absence of specific single-nucleotide polymorphisms (SNPs) in psoriasis-risk genes plays an important role. To date, SNPs located in *HLA-C, TNFAIP3*, *TNFA, IL12B*, *IL-23A* and *IL-23R TAP1* genes have been found to influence the response of psoriatic patients to anti-TNF-α or anti-IL-12/23 drugs[9-12].

Among psoriasis-related SNPs, the MHC class I allele *HLA-Cw6*, the strongest genetic risk variant predisposing to psoriasis, has been reported to associate with better response to the anti-IL-12/IL-23p40 drug ustekinumab[13, 14]. Similarly, anti-TNFs were found to be more effective in *HLA-Cw6*-positive patients, even though contrasting results have been reported[15]. A recent comparative study showed that

HLA-Cw6-negative patients are more likely to respond to adalimumab than to ustekinumab[15]. Moreover, the combination of *HLA-Cw6* allele with different genotypes, for instance those related to *IL12B* gene, determined optimal response to ustekinumab[16]. An interaction between the *HLA-Cw6* and *TNFAIP3* genotypes on disease improvement among patients treated with anti-TNFs has also been described[17]. To date, few pharmacogenetic studies on response to the anti-IL-17A drugs in the psoriatic population have been performed [18, 19].

Here, we report a pharmacogenomic study aimed at evaluating the simultaneous presence of SNPs in psoriasis-risk loci, associating with clinical response to secukinumab, in a cohort of 62 patients affected by moderate-to-severe plaque psoriasis. SNPs potentially predicting the response to secukinumab were identified.

1. MATERIALS & METHODS

2.1 Patients and ethics statement

Our study included 62 patients recruited between September 2015 and June 2018, at the Dermatology Unit, University of Rome “Tor Vergata". All patients were Caucasians, aged > 18 years with moderate-to-severe plaque-type psoriasis defined at enrolment by: Psoriasis Area Severity Index (PASI) score > 10, Body Surface Area (BSA) > 10%, Dermatology Life Quality Index (DLQI) > 10. Patients with a baseline PASI < 10, who presented involvement of sensitive areas were also included. The enrolled patients required biologic treatment with secukinumab, as failed to respond, had contraindications for, or did not tolerate at least one conventional treatment.

Secukinumab was administered following AIFA (Agenzia Italiana del Farmaco) criteria in a standard dosing regimen (300 mg subcutaneous, five times within 4 weeks followed by once monthly injections), used in monotherapy and not combined with conventional systemics or topical therapies.

For each patient, personal data, as well as anthropometric and clinical data were collected and were annotated in an electronic database specifically programmed and created *ad hoc* for the study. The severity of psoriasis and response to treatment were evaluated using the PASI score at baseline and, then, at follow-up visits on weeks 8, 16, 24, 40, 56, 64, 72, 88, and 100. Clinical efficacy was assessed in terms of the 75%, 90% and 100% improvement of PASI score compared to baseline (PASI75, PASI90 and PASI100). 2-ml blood samples were collected from each psoriatic patient to isolate DNA.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Tor Vergata University Ethics Committee (approval no. 20745, v. 25 Mar 2005). Thus, clinical data, as well as blood were collected from patients after written informed consent.

2.2 SNP analysis

DNA was extracted from blood by QIAcube system with QIAmp DNA kit (Qiagen, Hilden, Germany), and 10 ng were used for sequencing by NGS technology. The customized designed SNP panel was composed of *n* = 122 SNPs (Supplementary Table 2), present in *n* = 89 amplicons (size range 125-375 bp), potentially implicated in immune responses (antigen presentation, T-cell signalling, innate immunity), as well as inflammatory pathways (cytokine-dependent signalling) and skin barrier function. Sequencing of amplicons permitted the identification of additional 295 SNPs located nearby the primary SNPs. The SNP array analysis thus identified 417 genetic variants in total. The analysed SNPs were selected based on an extensive review of articles on the association between psoriasis and SNPs or response to biologics [9, 15, 20-27].

NGS was performed using the Ion GeneStudio™ S5 Plus platform (Thermo Fisher Scientific, Massachusetts, USA). Libraries were amplified by the Ion AmpliSeq™ Library kit Plus (Thermo Fisher) and quantified using the Qubit 4 Fluorometer and 2100 Bioanalyzer with dsDNA HS assay and High Sensitivity DNA kit (Thermo Fisher), respectively. Sequencing data were processed with Ion Torrent Suite software v.5.10.

Positive calls were selected with a read depth > 30X and allelic frequency of 0.3. Reads were aligned to human genome sequence (build GRCh37/hg19) and analysed using Variant Caller plugin. Variants' annotations were verified with ANNOVAR from the UCSC Genome Browser on hg19 assembly.

2.3 Statistical analysis

Drug response data were analysed by an intent-to-treat last observation carried forward method. SNPs that showed an identical pattern in patients have been merged to reduce the number of genetic variables that needed to be managed.

Differences between groups (allele-positive or -negative patients) based on the clinical response to secukinumab obtained at the different time-points of treatment were evaluated by χ^2 test. Univariate and multivariate logistic regression analysis were performed to combine genetic data or demographic variables, clinical factors and responses to secukinumab, expressed as PASI75, PASI90 or PASI100. The association between drug response and all the variables collected was estimated calculating the odds ratio (OR), its standard error and 95% confidence interval (CI), using the STATA 14.2 software (StataCorp, College Station, TX, USA). Deviation from null hypothesis was considered significant at p-value < 0.05.

CAP, based on the Bray-Curtis similarity matrix [28], was performed in order to assess multivariate differences in the genetic pattern of psoriatic population among the HLA-Cw6$^+$ or HLA-Cw6$^-$ patients showing high or low clinical responses to secukinumab. The canonical correlations were tested using 4999 random permutations of the genetic data, expressed as presence or absence of the SNPs. The analysed data matrix included 94 SNPs, since SNPs showing identical patterns in psoriatic patients were deleted. Moreover, distinctness of the four patient groups (HLA-Cw6$^+$ high-responders, HLA-Cw6$^+$ low-responders, HLA-Cw6$^-$ high-responders, HLA-Cw6$^-$ low-responders) was assessed using leave-one-out allocation success [29]. The product-moment correlations of the selected 94 SNPs with the two canonical discriminant axes (ρ1 and ρ2) were calculated, and only the most relevant correlation (i.e. $\sqrt{\rho 1^2 + \rho 2^2} > 0.35$) were considered as valuable and included in the plot. The multivariate analysis was carried out using PRIMER 6© v.6.1.5 and PERMANOVA +© v.1.0.1 software (PRIMER-E, Plymouth, UK).

2. RESULTS

3.1 SNPs in HLA-C and upstream region associate with clinical response to secukinumab

Participants' demographic and disease characteristics are summarized in Supplementary Table 1. At baseline, mean PASI was 18.9 ± 12.2, disease duration was 22.4 ± 14.9 years, and age at disease onset was 22.7 ± 12.2 years. Mean weight and body mass index (BMI) were 79.9 ± 17.5 and 26.8 ± 6.3, respectively. Most of the patients (74.5%) were naïve to biological therapy. Hypertension was the most frequent co-morbidity, together with obesity and type-2 diabetes. PASI follow-up scores were available for sixty (96.8%) patients at the central observational point (56 weeks) and for thirty-one (50%) at the last follow-up visit (100 weeks). The lack of efficacy (secondary lack of efficacy, defined as loss of PASI75 starting from week 16) was the main reason for discontinuation of the drug (7 out of 62 patients, 11.3 %).

In the primary analysis, we tested the influence of genetic variants predisposing to psoriasis on the response to secukinumab. Univariate logistic regression analysis between single independent variables (SNP status) and dependent variables, such as PASI75, PASI90 and PASI100 responses at weeks 8-100, identified eight SNPs in *HLA-C* and upstream region associating with an optimal response to secukinumab (Figure 1). Psoriatic patients carrying rs13191343 or rs13207315 SNPs in *HLA-C* promoter region (Figure 1a), more successfully achieved PASI75 and PASI90 end-points at weeks 16, 24, 40 and at week 56, as well as PASI100 at weeks 16 and 24 (statistical values in Supplementary Figure 1). For both SNPs, we observed the same pattern of presence in the psoriatic population and, thus, identical regression curves (Figure 1a). A third SNP in the *HLA-C* promoter region, the rs6900444, also influenced the response to secukinumab, as positive subjects reached faster PASI90 at weeks 8, 16, and week 24, when compared to negative patients (Supplementary Figure 2).

Of note, we observed a significant association between the *HLA-Cw6* psoriasis classical allele (rs1131118), and response to secukinumab (Figure 1b). In fact, allele-positive patients better achieved

PASI75 at weeks 16, 24 and 56, PASI 90 at weeks 24, 40 and 56, and PASI100 at weeks 8, 16 and 24 (statistical values in Supplementary Figure 3a). Other two SNPs co-segregating with *HLA-Cw6*, namely rs12189871 and rs4406273, showed the same pattern of presence in patients and, thus, identical regression curves (Figure 1b).

Rs12191877 or rs10484554 in HLA-C upstream region associated with a better response to secukinunab, as positive patients better reached PASI75 than allele-negative patients at weeks 8, 16, 24, 40, 56, and 88, PASI90 at weeks 16, 24, 40 and week 56, and PASI100 at weeks 16 and 24 (Figure 1c) (statistical values in Supplementary Figure 3b).

Association data and regression curves relative to rs12191877 and rs10484554 variants were identical, due to their identical status in patients. They were not detected in all the *HLA-Cw6*$^{+}$ subjects, even though they were previously described in linkage disequilibrium (LD) with *HLA-Cw6* [30, 31].

3.2 Optimal response to secukinumab associates with allelic variant status of *MICB-DT, DDX58* and *TYK2*

Significant results of association between SNP status and response to secukinumab were observed for three SNPs in *MICB-DT*, *DDX58* and *TYK2* genes. A strong association was found for rs9267325 in *MICB-DT*, whose absence in psoriatic patients determined a better response to secukinumab when compared to positive patients. Allele-negative patients faster achieved PASI75 at weeks 8, 16, 40 and 56, PASI90 at weeks 16, 24, 40, 56 and 88, and PASI100 achievement at weeks 40, 56 and 72 (Figure 2). In addition, rs9267325-negative patients achieved better PASI75, PASI90 and PASI100 if they did not previously receive other biological therapies. In fact, multivariate analysis revealed an association between rs9267325 and absence of previous treatments with response to secukinumab, in terms of PASI75 and PASI90 achievement (Table 1). The age also associated with a better response to secukinumab in absence of rs9267325 SNP (Table 1).

None of the analysed SNP associated with response to secukinumab in those patients showing particular sites of psoriasis manifestation (i. e. scalp, genital, palmo-plantar areas) (not shown).

We next observed that rs34085293 in *DDX58* or rs2304255 in *TYK2* were carried out by a subgroup of patients which highly responded to secukinumab, as they efficiently reached PASI100 and maintained high the response up to week 100 (Figure 3). Concerning rs34085293, PASI100 end-point was significantly reached by most of the allele-positive patients at weeks 24, 40, 56, 64 up to and 88 (Figure 3a). Similarly, the presence of rs2304255 SNP in *TYK2* gene determined PASI100 achievement at weeks 64, 72, 88 and 100 (Figure 3b).

Of note, both rs34085293 or rs2304255 polymorphisms were preferentially found in patients having the following demographic and clinical profile: males (10 out of 14 for rs34085293 and 10 out of 15 for rs2304255), early age of disease onset (13 out of 14 or 15 for rs34085293 or rs2304255, respectively), and naïve to previous biological treatment (12 of 14 for rs34085293 and 11 out of 15 for rs2304255), The other demographic and disease characteristics (age, BMI, disease duration, co-morbidities) seemed to be not associated with rs34085293 or rs2304255 SNP status.

Finally, the absence of two SNPs in *LTA* gene, namely rs1800683 and rs909253, determined a better response to secukinumab, in terms of PASI75 achievements at weeks 16, 24 and 40 (Supplementary Figure 4).

3.3 HLA-Cw6 status identifies specific SNP patterns in psoriatic patients associating with optimal response to secukinumab

In order to understand whether specific SNP patterns characterized patients depending on *HLA-Cw6* allele status and/or high or low clinical responses to secukinumab, we performed canonical analysis of principal coordinates (CAP). The analysis showed a significant clustering of patients belonging to HLA-Cw6^{+} and HLA-Cw6^{-} groups, and, specifically, in four established subgroups: HLA-Cw6^{+} high-

responders, HLA-Cw6^{+} low-responders, HLA-Cw6^{-} high-responders, and HLA-Cw6^{-} low-responders (Figure 4a). HLA-Cw6^{+} high-responders mainly distributed in the lower left quadrant of plot area (91.3%). The HLA-Cw6^{+} low-responder cluster was mostly found in the upper left quadrant (83.3%). On the other hand, low-responders (54.5%) and high-responders (58.3%) HLA-Cw6^{-} patients clustered in the lower and upper right quadrants, respectively, even though their distribution patterns partially overlapped (Figure 4a). Among HLA-Cw6^{-} patients, 5 out of 11 low-responders and 5 out of 13 high-responders did not segregate in their respective clusters, likely due to their similar genetic SNP pattern. It is noteworthy that the five HLA-Cw6^{-} low-responders clustering with HLA-Cw6^{-} high-responders showed severe obesity and discontinued treatment for loss of efficacy within the 2 years of observation. As shown in Figure 4a, HLA-Cw6^{+} and HLA-Cw6^{-} groups totally segregated along the *x*-axis and showed a distinct pattern of SNP presence. In particular, the DDX58_v2, HLA-Cw6_LD2-LD5, HLA-C_promoter1-promoter2, HLA-C exon2, HLA-Cw6_LD4, CCHCR1_v4-v5, HLA-Cw6_LD1-LD3, CDSN_v3, HLA-B27_LD1, CCHCR1_v2 and HLA-B-27_LD2 SNPs were mostly carried out by *HLA-Cw6*$^{+}$ patients (see Supplementary Table 2 for corresponding identification number). On the other hand, MICB-DT_v2, ERAP1_v1, ERAP1_v4, MICA_v2-v3, HLA-C_v8, ERAP1_v5 and ERAP1_v7, HLA-C_v5 and HLA-C_v7, HLA-C_v15, and RUNX3 variants characterized *HLA-Cw6*$^{-}$ patients. Importantly, most of the SNPs associating with *HLA-Cw6* were predominantly found in the high-responders, with the exception of HLA-B27_LD1, CCHCR1_v2 and HLA-B27_LD2, which were also present in low-responder group. Although HLA-Cw6_LD4, HLA-C exon2, CCHCR1_v4-5, and DDX58_v2 variants characterized HLA-Cw6^{+}patients of the high-responder group (Figure 4a), univariate regression analysis demonstrated significant association of these SNPs with optimal response to secukinumab only at discontinuous time-points of observation (data not shown). While MICB-DT_v2, ERAP1_v1, ERAP1_v4, MICA_v2-v3 variants were present in HLA-Cw6^{-} patients

showing moderate response to drug, HLA-C_v5, HLA-C_v7, HLA-C_v8, and HLA-C_v15, ERAP1_v5 and ERAP1_v7, as well as RUNX3 SNPs characterized *HLA-Cw6*$^-$ patients belonging to both low-responder and high-responder groups. (Figure 4a).

Of note, the IL23R_v4 and IL23R_v5 genetic variants were mutually exclusive with TRAF3IP2_v1 allele in patients. TRAF3IP2_v1 and IL23R_v4 or IL23R_v5 equally distributed in both *HLA-Cw6*$^+$ and *HLA-Cw6*$^-$ groups, with their representative arrows pointing to the area plot in the upper and lower quadrants, respectively, between the HLA-Cw6$^+$ and HLA-Cw6$^-$ groups (Figure 4a). Also, TYK2_v3 was found in patients of both HLA-Cw6$^+$ and HLA-Cw6$^-$ clusters, and it was mostly present in patients not showing TRAF3IP2_v1 allele.

In order to understand whether the IL23R_v4, IL23R_v5, TRAF3IP2_v1 and TYK2_v3 allele influenced the response to secukinumab of *HLA-Cw6*$^+$ and *HLA-Cw6*$^-$ patients, we performed univariate regression analysis of these SNPs and response to the drug, in terms of PASI90 achievement, using separate *HLA-Cw6*$^-$ or *HLA-Cw6*$^+$ patient databases. We found that IL-23R_v5, and not IL-23R_v4 allele presence significantly associated with response to secukinumab in *HLA-Cw6*$^+$ population (Figure 4b-c). PASI90 achievement in *HLA-Cw6*$^+$ population also significantly depended on TRAF3IP2_v1 allele absence and TYK2_v3 presence (Figure 4d-e). TRAF3IP2_v1 or TYK2_v3 alleles also significantly influenced PASI100 achievement by *HLA-Cw6*$^+$ patients at weeks 56, 64, 72 and 100 (data not shown). IL23R_v4, IL23R_v5, TRAF3IP2_v1 and TYK2_v3 allele status did not influence response of *HLA-Cw6*$^-$ population to secukinumab (Figure 4b-e).

The list of the SNPs significantly associating with a better secukinumab response and the number of psoriatic patients carrying these genetic variants are summarized in Supplementary Table 3.

3. DISCUSSION

The genetic basis of psoriasis has long been recognized, and, thanks to genome-wide association studies and linkage scans, more than sixty susceptibility regions predisposing to psoriasis have been identified[21, 22, 24, 25, 27, 32, 33]. The major genetic determinants of psoriasis reside in psoriasis susceptibility (*PSORS)1* locus, mapping on chromosome 6p21. This region spans approximately 250 kb within the MHC class I region and contains nine genes, including *HLA-C*, *HLA-B, TNFA, LTA,* and *MICB*, together with non-protein coding genes and pseudogenes[34]. Although *HLA-Cw6* is itself considered the causal *PSORS1* allele, over one-hundred *HLA-C* alleles and several SNPs within *HLA-C* promoter region have been identified[35]. Other psoriasis-risk SNPs were identified in additional *PSORS* loci, in genes involved in Th17/Th1 responses, innate immunity and inflammatory pathways, as well skin barrier and antigen presentation functions[1].

In the last decade, several pharmacogenetic studies allowed the identification of polymorphisms potentially predicting the clinical response of psoriatic patients to the anti-TNF-α adalimumab, and to the anti-IL-12/IL-23 ustekinumab[10, 11, 13, 15, 36]. On the contrary, pharmacogenetic studies on IL-17 blockers are scarce and contrasting. In fact, secukinumab showed good efficacy independently of *HLA-C*06:02* allele in the phase-IIIb SUPREME study[19, 37], whereas, in a real-life setting, it was shown to be more efficacious in *HLA-C*06:02*-positive than in negative patients[38].

In the present study, we identified a set of psoriasis-risk SNPs associating with an excellent response to secukinumab (Figure 5). Among HLA-C SNPs, three (rs13191343, rs13207315 and rs6900444) were present at – 1268, – 1209 and at – 1196 bp from the transcription start site of *HLA-C*. The first two are strictly close, and positioned in *HLA-C* promoter region containing three putative binding sites for the Sp1 transcription factor, which could be involved in the IL-17-dependent positive regulation of *HLA-C*. Indeed, a previous work investigated on possible effects of other two SNPs in *HLA-C* promoter virtually abolishing the response to TNF-α and IFN-γ, and pointed out the

significance of SNP influence on the regulation of *HLA-C* by cytokines in psoriasis[39]. The other HLA-C variants associating with secukinumab response include the *HLA-Cw6* psoriasis classical allele (rs1131118), and rs12189871 and rs4406273. While rs1131118 is present in the exon 3 of *HLA-C* gene, rs12189871 and rs4406273 are located 12 kb and 26 kb upstream of *HLA-C* (Figure 5). Of note, rs4406273 SNP maps within a region containing two overlapping sequences, namely LINC02571 and LOC112267902, generating two long non-coding RNA (lncRNA) with potential regulatory functions on *HLA-C*[40]. The pattern of presence of rs1131118 in *HLA-C* exon 3 and rs12189871 or rs4406273 in *HLA-C* intergenic region was identical in all psoriatic patients, indicating that these allelic variants co-segregate, even though they are distant from each other. Rs12191877 or rs10484554, located 13 kb and 34 kb upstream of *HLA-C* (Figure 5) also co-segregate, and determined a better response to secukinumab treatment.

Although no functional evidence correlating the presence of *HLA-Cw6* variant and response to secukinumab exist, it is plausible that this allele allows the presentation of epitopes present in different putative autoantigens, such as the cathelecidin LL37, which is efficiently recognized by circulating $CD8^+$ T cells with a psoriasis-like cytokine profile (IFN-γ^{high} and IL-17^{high})[41]. On the other hand, SNPs present in HLA-C regulatory regions, spanning the HLA-C promoter and upstream regions, could influence the expression levels of HLA-C class I molecules on immune and resident skin cells, and, in turn, the expansion rate of $CD8^+$ IL-17-producing T cells. Future studies exploring the functional role of specific HLA-C alleles in IL-17-dependent immune responses will be fundamental not only to unveil their pathogenic activity in psoriasis but also to understand why specific HLA-C haplotypes effectively respond to the anti-IL-17 treatments.

Significant results of association were also observed for rs9267325 in *MICB-DT* (Figure 5), whose absence in psoriatic patients determined a better response to secukinumab, with a further greater likelihood of reaching PASI100 if patients did not undergo to previous biological treatments.

Interestingly, rs9267325 SNP localizes nearby *MICB*, within *MICB-DT* (Figure 5), from which a divergent regulatory RNA or lncRNA is generated. As consequence of absence of rs9267325, it is plausible that MICB-DT RNA cannot appropriately regulate the expression levels of *MICB* mRNA[42]. The identification of association of rs9267325 with secukinumab response is particularly intriguing since *MICB* encodes a MHC class I-related protein with potential immunological functions on IL-17-producing and NKG2D-bearing NK and $CD8^+$ T cells[43].

Our pharmacogenomic analysis also revealed an association with two co-segregating SNPs of *LTA* (rs1800683 and rs909253) (Figure 5), potentially present in the 5' untranslated region of *LTA* mRNA, and, thus, in a presumably regulatory region. Expression levels of lymphotoxin-α could influence innate immune responses in psoriatic skin, especially during the early phase of disease development[44].

Importantly, we identified two SNPs in *TYK2* (rs230425) and *DDX58* (rs34085293) (Figure 5), in a subgroup of super-responder patients achieving and maintaining PASI100 up to weeks 88 and 100. Most of the rs230425-positive super-responders were also HLA-$Cw6^+$. TYK2 and DDX58 have been initially described as mediators of anti-viral and innate immune responses. While TYK2 is a tyrosine kinase belonging to Janus kinase protein family, which associates with type I and type II cytokine receptors, including type-I IFN receptors, DDX58 is a protein involved in viral double-stranded RNA recognition and type-I IFN production. Although both molecules have antiviral activity, recent evidence show TYK2 and DDX58 involvement in IL-23/IL-17 axis by inducing IL-23 and regulating IL-23-mediated pathways[45, 46]. While rs34085293 maps in *DDX58* intergenic region and the impact of its presence is unpredictable, rs2304255 is positioned in exon 8 of *TYK2* and determines a missense substitution in the protein. Our association data of rs34085293 and rs2304255 with the clinical effect of secukinumab in the super-responder population, together with evidence on TYK2 and DDX58 involvement in IL-23/IL-17 axis, strongly suggest the importance of these pathogenic pathways in the response to anti-IL-17 drug.

A growing number of evidence showed that HLA-Cw6^{+} and HLA-Cw6^{-} plaque psoriasis represents biologically distinct pathologies and endotypes[47]. *HLA-Cw6* is associated with phenotypic features, including early-onset psoriasis, guttate lesions, as well as arm, leg and trunk involvement. In addition, it is now well-established that HLA-Cw6^{+} patients have different profiles of response to biological drugs[15, 36].

Our study supports the notion that HLA-Cw6 status efficiently stratifies psoriatic patients, showing HLA-Cw6^{+} patients a specific psoriasis-risk SNP pattern, as well as optimal response to secukinumab. We found that HLA-Cw6^{+} and HLA-Cw6^{-} patients differently clustered in CAP plots as consequence of their different genotypes. SNPs characterizing each group mainly localized in the HLA-C upstream region, with variants present in HLA-Cw6^{+} patients being mutually exclusive with those found in HLA-Cw6^{-} patients. Nevertheless, most of the SNPs associating or not with *HLA-Cw6* were predominantly located in genes of *PSORS1* locus, indicating the relevance of this region in the predisposition of all patients to psoriasis.

Importantly, HLA-Cw6 status also identified specific SNP patterns associating with clinical response to secukinumab. For instance, most of the SNPs characterizing HLA-Cw6^{+} patients were highly represented in the high-responder subpopulation, thus confirming data obtained by univariate regression analysis. Concerning SNPs typical of HLA-Cw6^{-} patients, MICB-DT_v2 variant (rs9267325) was present in the group showing moderate response to the drug, accordingly to the findings that its absence determined a better response to secukinumab in regression models.

Of note, despite the presence of IL23R_v5, TYK2_v3, and TRAF3IP2_v1 variants in both groups, only HLA-Cw6^{+} patients responded significantly better to secukinumab depending on IL23R_v5 and TYK2_v3 presence or TRAF3IP2_v1 allele absence. The functional significance of these associations could be related to the hyperactivation of IL-23- and IL-17 pathways in psoriatic skin, being IL-23R,

TYK2 and TRAF3IP2 all fundamental for type-17 T-cell responses and IL-17 signaling in target cells[2, 46]. Since IL23R_v5 and TRAF3IP2_v1 SNPs map, respectively, within a regulatory region of *IL23R* and in a sequence generating the LOC107986521 lncRNA, they could influence IL-23R and TRAF3IP2 expression levels.

4. CONCLUSIONS

In this pharmacogenomic, real-life study, we identified a set of SNPs associating with optimal response to secukinumab in a cohort of 62 patients affected by psoriasis. Despite the limited sample size, our study is the first analyzing the simultaneous presence of a high number of genetic variants in patients undergone anti-IL-17A treatment. SNP panel included polymorphisms highly represented in the psoriatic population (i. e. HLA-C variants), as well as rare genetic variants (i. e. IL-36G and CARD14) having a low frequency in psoriasis. To unveil their association with anti-IL-17A treatment, the latter genotypes need to be investigated in large cohorts of patients, as well as in different clinical subtypes characterized by specific haplotypes.

Among common genetic variants, *HLA-Cw6* risk-allele strongly influenced response to the IL-17A blocker, confirming the relevance of this genetic variant for treatment efficacy observed with other biologics. We also identified HLA-C-related alleles, and *MIC-DT*, *DDX58* and *TYK2* SNPs significantly influencing response to the drug. In addition, we found that HLA-Cw6 status was associated with specific SNP patterns, mainly represented by polymorphisms of *HLA-C* genic and intergenic regions and *PSORS1* locus.

Thus, the assessment of *HLA-Cw6* genotype, together with other allelic variants of different genes involved in intersected pathogenic pathways, could be helpful to better classify patients and to predict treatment response to secukinumab.

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Declaration of Interests

L Bianchi has served as a speaker and as a consultant for Abbvie, Novartis, Janssen-Cilag, Pfizer, UCB, and Leo-Pharma outside the submitted work. G Girolomon has been principal investigator in clinical trials sponsored by and/or and has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Celgene, Celltrion, Eli-Lilly, Genzyme, Leo Pharma, Menlo therapeutics, Novartis, OM Pharma, Pfizer, Regeneron, Samsung, Sandoz and UCB. The 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 contributions

Conceptualization: CA, MG, MT, SM, MM; Resources: MG, MT, LB, SP, TG, MA; Formal Analysis and Investigation: MM, MG, GLS; Methodology: CS; Funding Acquisition: CA, SM, GG; Supervision: CA, MG, MT, SM; Writing original draft: CA; Writing review & editing: CA, SM, GG, MM, MG, MT.

All Authors gave the final approval of the version to be published, and all Authors agree to be accountable for all aspects of the work.

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Reviewer Disclosures
Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

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FIGURE LEGENDS

Fig. 1. Association analysis between rs13191343, rs13207315, rs1131118, rs12189871, rs4406273, rs12191877, and rs10484554 SNPs and clinical responses to secukinumab treatment. Univariate logistic regression analysis was performed to evaluate the association between (**A**) rs13191343 (HLA-C_promoter1) or rs13207315 (HLA-C_promoter2), (**B**) rs1131118 (HLA-Cw6), rs12189871 (HLA-Cw6_LD1) or rs4406273 (HLA-Cw6_LD3), and (**C**) rs12191877 (HLA-Cw6_LD2) or rs10484554 (HLA-Cw6_LD5) with the clinical response to secukinumab after 8, 16, 24, 40, 56, 64, 72, 88 and 100 weeks of treatment, in a cohort of patients (n = 62) affected by moderate-to-severe psoriasis. Graphs show the percentage and the number of patients (n Pz) carrying (SNP-POS, dark gray line) or not (SNP-NEG, gray line) the SNPs and achieving 75% reduction of PASI score (PASI75), 90% reduction of PASI (PASI90) and 100% reduction (PASI100). rs13191343 and rs13207315, rs1131118, rs12189871 and rs4406273, as well as rs12191877 and rs10484554 showed the same pattern of presence/absence in the psoriatic population and, thus, identical logistic regression curves. *p value < 0.05 were considered significant.

Fig. 2. Association analysis between rs9267325 SNP and clinical response to secukinumab. Rs9267325 (MICB-DT_v2)-negative (SNP-NEG, gray line) patients reached a significant better response to secukinumab than positive patients (SNP-POS, dark gray line), in terms of achievement of

PASI75 (**A**), PASI90 (**B**) and PASI100 (**C**), as evaluated by logistic regression analysis. The univariate logistic regression analysis is also summarized in the forest plot in the lower panel. The condition of good response to secukinumab is more likely to occur in the group of patients not carrying the allele, as indicated by the odds ratio (OR) < 1. Squares on the *x*-axis shows odd ratio (OR), squares indicate OR estimates for each observation point and the error bars represent 95% confidence interval (CI). **p* value < 0.05 were considered significant and indicated in font bold.

Fig. 3. Rs34085293 and rs2304255 SNPs associate with an optimal clinical response to secukinumab treatment. The presence of rs34085293 (DDX58_v1) and rs2304255 (TYK2_v3) variants determined an optimal response to secukinumab treatment at several time-points of observation. The upper and lower graphs show respectively the percentage and the number (*n* Pz) of DDX58_v1-positive (SNP-POS, dark gray line) and -negative (SNP-POS, gray line) subjects (**A**) or TYK2_v3-positive (SNP-POS, dark gray line) and -negative (SNP-POS, gray line) (**B**) patients achieving 100% reduction in the PASI score (PASI100). The relative univariate logistic regression analyses are summarized in forest plots in the right panels, where the *x*-axis shows odd ratio (OR), squares indicate OR estimates for each observation point and the error bars represent 95% confidence interval (CI). **p* value < 0.05 were considered significant and indicated in font bold.

Figure 4. HLA-Cw6 status identifies specific SNP patterns in psoriatic patients correlating with clinical response to secukinumab. Clustering of patients based on presence of SNPs and response to secukinumab was performed by CAP on a cohort of psoriatic patients (*n* = 53), classified as high responders to secukinumab (PASI90 or PASI100 achievement at week 56) or low responders (unsatisfactory responses or achievement of PASI75 or less at week 56). (**A**) CAP ordination plot shows a significant clustering of psoriatic patients belonging to HLA-Cw6^{+} and HLA-Cw6^{-} groups along *x*-axis, and, in particular, to four established subgroups: HLA-Cw6^{+} high-responders (downward triangles), HLA-Cw6^{+} low-responders (triangles), HLA-Cw6^{-} high-responders (diamonds), and HLA-

Cw6$^-$ low-responders (squares) to secukinumab. The percentage of patients carrying similar SNP profiles, based on the response to secukinumab and HLA-Cw6 status, and relative to leave-one-out allocation of observations to groups, are shown in panel **A**. The length of each vector line corresponds to the strength of the correlation and direction for each SNP (squared canonical correlations $\delta_1^2 = 0.89$ and $\delta_2^2 = 0.25$; $p = 0.0002$; 69.8% of sampling units correctly classified). Univariate logistic regression analysis was employed to evaluate the association between rs1004819 (IL23R_v4) (**B**), rs2201841 (IL23R_v5) (**C**), rs71562288 (TRAF3IP2_v1) (**D**) or rs2304255 (TYK2_v3) (**E**) and PASI90 response at 8, 16, 24, 40, 56, 64, 72, 88 and 100 weeks of treatment, in HLA-Cw6$^+$ (left column) and HLA-Cw6$^-$ (right column) patient groups. **p* values < 0.05 were considered significant.

Figure 5. Scheme of SNPs associated with response to secukinumab and relative positions on chromosomes 6, 9 and 19. A schematic representation of all the identified SNPs associating with optimal response to secukinumab, and their relative positions (vertical lines) within gene and adjacent regions of chromosomes 6, 9 and 19 are shown. While HLA-C-related SNPs, together with those present in *MIC-DT* (rs9267325) and *LTA* (rs1800683 and rs909253), map within *PSORS*1 locus of chromosome 6, DDX58_v1 (rs34085293) and TYK2_v3 (rs2304255) SNPs localize in chromosome 9 and 19, respectively. Black boxes with continuous lines schematically represent exons and introns of genes, whereas dashed lines the intergenic regions. Gray bars indicate characterized or predicted lncRNAs, and arrows show the direction of transcription.

Table 1. Multivariate logistic regression analysis (step-wise analysis) of predictors of PASI response after treatment with secukinumab

Variable	OR [95% CI]	*p*-value
PASI75		
8 weeks		
Previous biological therapy	0.28 [0.13-0.59]	0.0001
MICB-DT_v2 (rs9267325)	0.15 [0.03-0.82]	
40 weeks		
Previous biological therapy	0.28 [0.13-0.59]	0.0001
MICB-DT_v2 (rs9267325)	0.15 [0.03-0.82]	
56 weeks		
Previous biological therapy	0.22 [0.09-0.53]	0.0001
MICB-DT_v2 (rs9267325)	0.06 [0.01-0.38]	
PASI90		
16 weeks		
Previous biological therapy	0.35 [0.17-0.71]	0.0004
MICB-DT_v2 (rs9267325)	0.17 [0.03-0.79]	
24 weeks		
Age (*per* year)	0.89 [0.82-0.96]	0.0001
MICB-DT_v2 (rs9267325)	0.12 [0.03-0.61]	
40 weeks		
Previous biological therapy	0.28 [0.13-0.60]	0.0001
MICB-DT_v2 (rs9267325)	0.06 [0.01-0.33]	
56 weeks		
Previous biological therapy	0.42 [0.19-0.96]	
Age (*per* year)	0.93 [0.86-0.99]	0.0001
MICB-DT_v2 (rs9267325)	0.12 [0.02-0.59]	
PASI100		
40 weeks		
Previous biological therapy	0.37 [0.15-0.89]	
Age (*per* year)	0.93 [0.87-0.98]	0.0001
MICB-DT_v2 (rs9267325)	0.19 [0.04-0.90]	
72 weeks		
Age (*per* year)	0.92 [0.87-0.98]	0.0001
MICB-DT_v2 (rs9267325)	0.11 [0.02-0.78]	

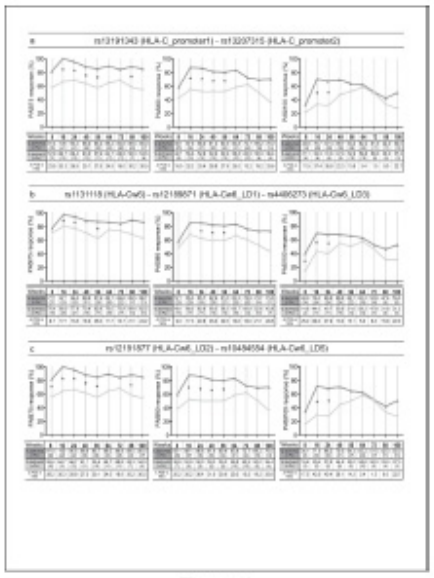


Figure 1

Figure 1

180x251mm (300 x 300 DPI)

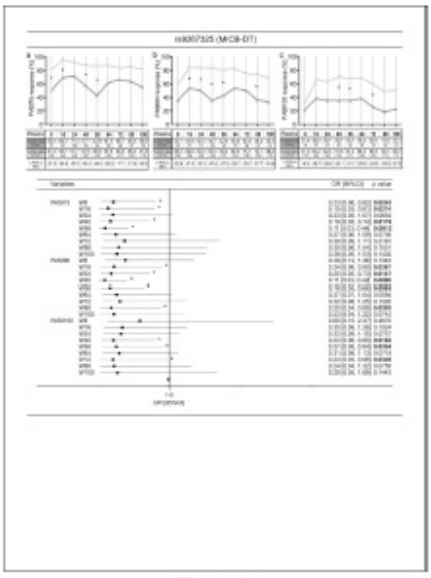


Figure 2

Figure 2

180x251mm (300 x 300 DPI)

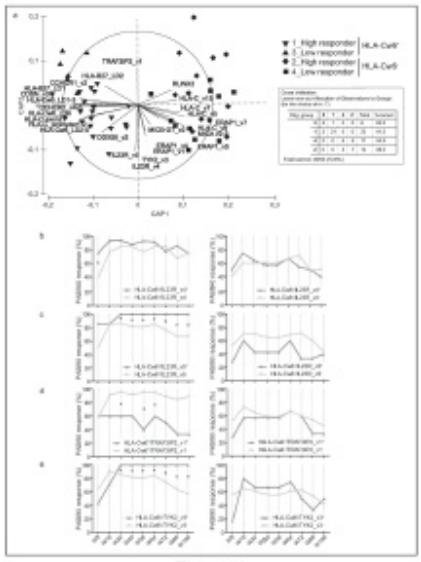


Figure 4

Figure 4

184x258mm (300 x 300 DPI)

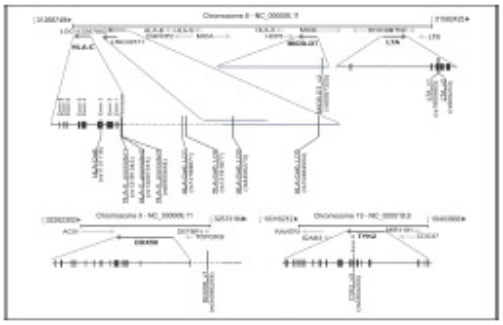
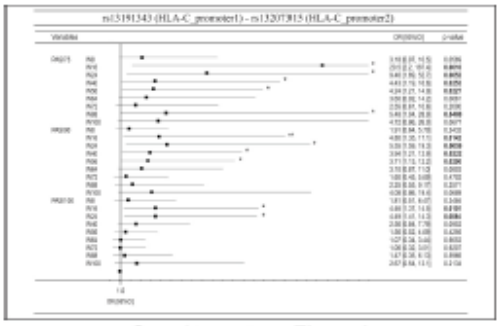


Figure 5

Figure 5

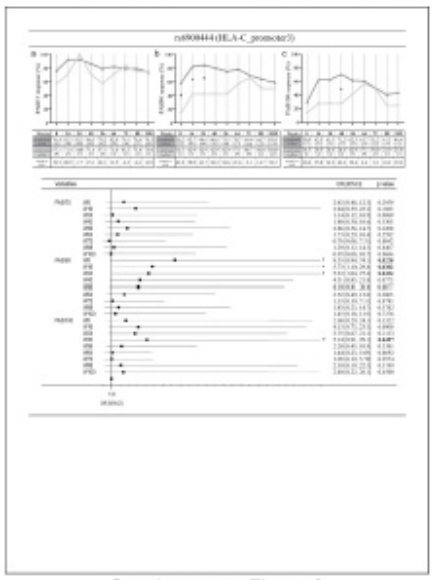
181x127mm (600 x 600 DPI)



Supplementary Figure1

Supplementary Figure 1

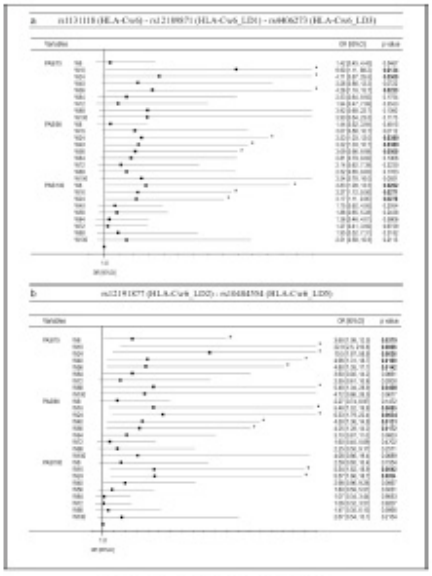
181x126mm (600 x 600 DPI)



Supplementary Figure 2

Supplementary Figure 2

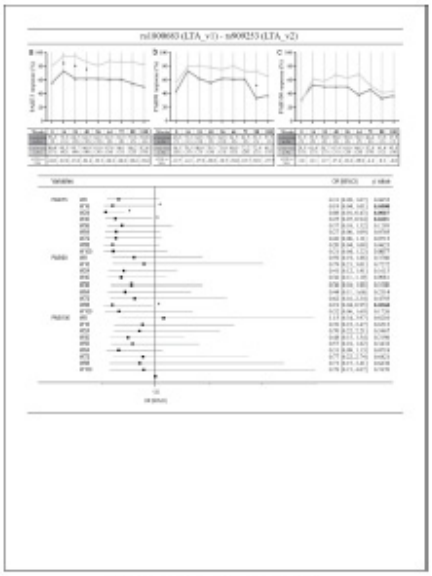
180x250mm (300 x 300 DPI)



Supplementary Figure 3

Supplementary Figure 3

180x251mm (600 x 600 DPI)



Supplementary Figure 4

Supplementary Figure 4

180x251mm (300 x 300 DPI)

Supplementary Table 1. Demographic and disease characteristics of patients (*n* = 62)

Characteristics	
Male/female (*n*)	41/21
	Mean ± SD (range)
Age (*years*)	45.1 ± 13.1 (22-76)
PASI at baseline	18.9 ± 12.2 (8.0-56.7)
PASI at follow-up (*n*)	
Week 8 (62)	3.56 ± 4.99 (0-30)
Week 16 (59)	1.58 ± 4.18 (0-30)
Week 24 (62)	2.28 ± 6.86 (0-52)
Week 40 (62)	2.57 ± 7.09 (0-52)
Week 56 (60)	3.11 ± 7.91 (0-52)
Week 64 (54)	3.20 ± 7.95 (0-52)
Week 72 (49)	3.53 ± 8.00 (0-52)
Week 88 (38)	4.22 ± 8.79 (0-52)
Week 100 (31)	4.78 ± 9.63 (0-52)
Duration of disease (*years*)	22.4 ± 14.9 (3-57)
Age at disease onset (*years*)	22.7 ± 12.2 (3-62)
Weight (*kg*)	79.9 ± 17.5 (55-133)
BMI (kg/m^2)	26.8 ± 6.3 (18.9-41.8)
Biologics before anti-IL-17A therapy	*n* (%)
0 prior biologics	46 (74.5)
1 prior biologics	6 (9.5)
2 prior biologics	4 (6.5)
≥ 3 prior biologics	6 (9.5)
Comorbidities	28
Hypertension	17
Type-2 diabetes mellitus	6
Hyperlipidemia	3
Depression	1
Obesity (BMI ≥ 30.0-34.9 kg/m^2)	19

Antigen presentation					
Genome position	**Gene**	**REF/ALT**	**SNP name**	**dbSNP ID**	**MAF**
Chr5:96101944	ERAP1	A/G	ERAP1_v1	rs27524	0.6296
Chr5:96101959	ERAP1	C/T	ERAP1_v2	rs27525	0.4532
Chr5:96118852	ERAP1	G/C	ERAP1_v3	rs27044	0.7158
Chr5:96124330	ERAP1	T/C	ERAP1_v4	rs30187	0.6491
Chr5:96124447	ERAP1	G/C	ERAP1_v5	rs30186	0.7886
Chr5:96124453	ERAP1	A/G	ERAP1_v6	rs11743410	0.1245
Chr5:96139250	ERAP1	C/G	ERAP1_v7	rs26653	0.6660
Chr6:31155785	HLA-C region	G/C	HLA-B27_LD1	rs1265181	0.2115
Chr6:31239108	HLA-C	T/A	**HLA-Cw6**	**rs1131118**	0.3143
Chr6:31239506	HLA-C	C/G	HLA-C exon2	rs1050414	0.1201
Chr6:31241109	HLA-C region	C/T	**HLA-C_promoter1**	**rs13191343**	0.1394
Chr6:31241127	HLA-C region	T/C	**HLA-C_promoter2**	**rs13207315**	0.1429
Chr6:31241182	HLA-C region	C/T	**HLA-C_ promoter3**	**rs6900444**	0.4937
Chr6:31251924	HLA-C region	C/T	**HLA-Cw6_LD1**	**rs12189871**	0.0904
Chr6:31252925	HLA-C region	C/T	**HLA-Cw6_LD2**	**rs12191877**	0.13253
Chr6:31252951	HLA-C region	G/T	HLA-C_v2	rs116350468	0.0357
Chr6:31253034	HLA-C region	T/G	HLA-C_v3	rs115727572	0.0357
Chr6:31266085	HLA-C region	C/G	HLA-C_v4	rs17192533	0.1028
Chr6:31266090	HLA-C region	G/A	**HLA-Cw6_LD3**	**rs4406273**	0.0775
Chr6:31266117	HLA-C region	A/C	HLA-C_v5	rs2524095	0.5689
Chr6:31266151	HLA-C region	G/T	HLA-C_v6	rs7761855	0.0633
Chr6:31266190	HLA-C region	A/G	HLA-C_v7	rs2853922	0.6029
Chr6:31266207	HLA-C region	CA/TG	HLA-C_v8	rs386698994	MNV
Chr6:31274380	HLA-C region	T/C	HLA-Cw6_LD4	rs9264942	0.3654
Chr6:31274449	HLA-C region	C/A	HLA-C_v9	rs35647108	0.0671
Chr6:31274513	HLA-C region	A/G	HLA-C_v10	rs6931873	0.2109
Chr6:31274518	HLA-C region	T/TCGGGGAGTCCAGCAGGTCC	HLA-C_v11	rs28383849	INS
Chr6:31274555	HLA-C region	C/T	**HLA-Cw6_LD5**	**rs10484554**	0.1442
Chr6:31274580	HLA-C region	C/G	HLA-C_v12	rs184149624	0.0217
Chr6:31274582	HLA-C region	A/G	HLA-C_v13	rs9348865	0.3769
Chr6:31274584	HLA-C region	AA/A	HLA-C_v14	rs147538049	0.0439
Chr6:31274586	HLA-C region	A/G	HLA-C_v15	rs9348865	0.3769
Chr6:31274619	HLA-C region	A/G	HLA-C_v16	rs9264944	0.2350
Chr6:31274634	HLA-C region	T/C	HLA-C_v17	rs9264946	0.2053
Chr6:31344583	HLA-B region	A/G	HLA-B*27_LD2	rs13202464	0.0696
Chr6:31362120	MICA region	G/A	MICA_v1	rs66609536	0.2539
Chr6:31377047	MICA	C/T	MICA_v2	rs6910087	0.1305
Chr6:31377086	MICA	C/G	MICA_v3*	rs528265306	0.0070
Chr6:31431780	HCP5	T/G	HCP5_v1	rs2395029	0.0359
Chr6:31431820	HCP5	C/T	HCP5_v2	rs2243621	0.1611
Chr6:31431874	HCP5	G/T	HCP5_v3	rs2395030	0.0474
Chr6:31461372	MICB-DT	A/T	MICB-DT_v1	rs2507971	0.6052
Chr6:31461492	MICB-DT	G/C	**MICB-DT_v2**	**rs9267325**	0.1409

Supplementary Table 2. List of the analyzed SNPs

Skin barrier function

Genome position	Gene	REF/ALT	SNP name	dbSNP ID	MAF
Chr1:152550018	LCE region	T/G	LCE_v1	rs4085613	0.6370
Chr1:152551276	LCE3B region	A/G	LCE3B	rs4112788	0.6369
Chr1:152590187	LCE region	C/T	LCE_v2	rs6677595	0.6361
Chr1:152591142	LCE region	A/C	LCE_v3	rs1886734	0.6369
Chr1:152592184	LCE region	C/T	LCE_v4	rs4845454	0.6376
Chr1:152593549	LCE region	C/T	LCE_v5	rs10888503	0.6442
Chr1:152778526	LCE1C	C/T	LCE1C	rs6701216	0.1467
Chr6:31084163	CDSN	A/G	CDSN_v1	rs3132554	0.5235
Chr6:31084170	CDSN	A/C	CDSN_v2	rs1042127	0.1935
Chr6:31084191	CDSN	T/C	CDSN_v3	rs33941312	0.0249
Chr6:31084288	CDSN	T/C	CDSN_v4	rs1042126	0.5185
Chr6:31084787	CDSN	A/G	CDSN_v5	rs707913	0.2139
Chr6:31084792	CDSN	C/T	CDSN_v6	rs3130983	0.5186
Chr6:31110391	CCHCR1	G/C	CCHCR1_v1	rs1576	0.3461
Chr6:31112737	CCHCR1	C/A	CCHCR1_v2	rs130079	0.2491
Chr6:31114182	CCHCR1	A/G	CCHCR1_v3	rs746647	0.3220
Chr6:31122482	CCHCR1	G/A	CCHCR1_v4	rs130076	0.2185
Chr6:31122500	CCHCR1	G/A	CCHCR1_v5	rs130065	0.2083
Chr9:110817020	KLF4 region	A/G	KLF4	rs10979182	0.4154

Innate immunity

Genome position	Gene	REF/ALT	SNP name	dbSNP ID	MAF
Chr2:113736296	IL36G	G/T	IL36G _v1	rs28947206	0.0002
Chr2:113736325	IL36G	C/T	IL36G _v2	rs28947207	0.0002
Chr2:113739563	IL36G	T/C	IL36G _v3	rs28947211	0.0003
Chr2:163124051	IFIH1	C/T	IFIH1	rs1990760	0.6002
Chr6:31540071	LTA	G/A	**LTA_v1**	**rs1800683**	0.3257
Chr6:31540313	LTA	A/G	**LTA_v2**	**rs909253**	0.3326
Chr6:31542482	LTA region	C/T	LTA_v3	rs1799724	0.1149
Chr8:7272439	DEFB4B	G/A	DEFB4B_v1	rs2740091	0.1781
Chr8:7273050	DEFB4B	T/C	DEFB4B_v2	rs73661358	0.1517
Chr9:32534714	DDX58 region	T/G	**DDX58_v1**	**rs34085293**	0.1410
Chr9:32534851	DDX58 region	G/A	DDX58_v2	rs657454	0.6309
Chr12:56737973	STAT2	A/G	STAT2	rs2066808	0.0671
Chr19:10469975	TYK2	A/C	TYK2_v1	rs12720356	0.0883
Chr19:10472933	TYK2	A/G	TYK2_v2	rs280519	0.5167
Chr19:10475649	TYK2	C/T	**TYK2_v3**	**rs2304255**	0.0758
Chr19:10475652	TYK2	C/A	TYK2_v4	rs2304256	0.2850
Chr20:30045393	DEFB123 region	G/A	DEFB123	rs6088273	0.6282

Cytokine-dependent pathways and T-cell signaling

Genome position	Gene	REF/ALT	SNP name	dbSNP ID	MAF
Chr1:12252955	TNFRSF1B	T/G	TNFRSF1B_v1	rs1061622	0.2367
Chr1:12267265	TNFRSF1B	A/G	TNFRSF1B_v2	rs1061624	0.5554
Chr1:12267292	TNFRSF1B	C/T	TNFRSF1B_v3	rs3397	0.6393
Chr1:25293084	RUNX3 region	T/C	RUNX3	rs7536201	0.5437
Chr1:67600686	IL23R region	G/T	IL23R_v1	rs12044149	0.2526
Chr1:67611613	IL23R	G/A	IL23R_v2	rs4655683	0.3397
Chr1:67658803	IL23R	G/A	IL23R_v3	rs72676067	0.2915
Chr1:67670213	IL23R	G/A	IL23R_v4	rs1004819	0.2987
Chr1:67694202	IL23R	A/G	IL23R_v5	rs2201841	0.3059
Chr1:67705900	IL23R	G/A	IL23R_v6	rs41313262	0.0160
Chr1:67705958	IL23R	G/A	IL23R_v7	rs11209026	0.0656
Chr3:101576029	NFKBIZ	T/TACTTTTAGAA AGCTTTAATAACC	NFKBIZ_v1	rs3217713	0.7714
Chr3:101615826	NFKBIZ region	G/T	NFKBIZ_v2	rs4683946	0.1998

Chr3:101663555	NFKBIZ region	A/G	NFKBIZ_v3	rs7637230	0.2087
Chr5:150467189	TNIP1	G/C	TNIP1_v1	rs2233278	0.0507
Chr5:150476004	TNIP1 region	T/C	TNIP1_v2	rs1024995	0.1124
Chr5:158742950	IL12B	T/G	IL12B_v1	rs3212227	0.2029
Chr5:158750769	IL12B	C/T	IL12B_v2	rs3213094	0.2048
Chr5:158759900	IL12B region	A/G	IL12B_v3	rs2546890	0.4861
Chr5:159912418	MIR146A	C/G	MIR146A	rs2910164	0.7600
Chr6:31543031	TNFα region	G/A	TNFα_v1	rs1800629	0.1624
Chr6:31543101	TNFα region	G/A	TNFα_v2	rs361525	0.0529
Chr6:31543827	TNFα	G/A	TNFα_v3	rs1800610	0.0869
Chr6:31543943	TNFα	G/GTGAA	TNFα_v4	rs374501689	DEL
Chr6:52101739	IL17F	T/C	IL17F_v1	rs56499381	0.0473
Chr6:52101758	IL17F	C/T	IL17F_v2	rs11465553	0.0407
Chr6:52101844	IL17F	T/C	IL17F_v3	rs2397084	0.0942
Chr6:111577761	TRAF3IP2 region	A/G	TRAF3IP2_v1	rs71562288	0.0917
Chr6:111673714	TRAF3IP2 region	T/C	TRAF3IP2_v2	rs240993	0.7282
Chr6:111913262	TRAF3IP2 region	C/T	TRAF3IP2_v3	rs33980500	0.0786
Chr6:111922720	TRAF3IP2 region	A/G	TRAF3IP2_v4	rs13210247	0.0662
Chr6:138196066	TNFAIP3	T/G	TNFAIP3_v1	rs2230926	0.0348
Chr6:138197824	TNFAIP3	C/T	TNFAIP3_v2	rs582757	0.7371
Chr6:138199417	TNFAIP3	G/T	TNFAIP3_v3	rs610604	0.6745
Chr9:117552885	TNFSF15	T/C	TNFSF15_v1	rs3810936	0.6912
Chr9:117558703	TNFSF15	C/T	TNFSF15_v2	rs6478108	0.6693
Chr9:117566440	TNFSF15	A/G	TNFSF15_v3	rs4263839	0.6850
Chr9:117568766	TNFSF15 region	A/G	TNFSF15_v4	rs6478109	0.6794
Chr12:6450945	TNFRSF1A	T/C	TNFRSF1A	rs767455	0.4326
Chr16:11365500	SOCS1 region	C/T	SOCS1	rs367569	0.2777
Chr17:26106675	NOS2	A/G	NOS2_v1	rs4795067	0.3519
Chr17:26124908	NOS2	G/A	NOS2_v2	rs28998802	0.1520
Chr17:78157811	CARD14	T/G	CARD14	rs146214639	0.0023
Chr21:36470865	RUNX1 region	C/T	RUNX1	rs8128234	0.2114
Chr22:17565035	IL17RA region	G/A	IL17RA	rs4819554	0.8084

The SNP panel was composed of n = 122 SNPs located in genes predisposing to psoriasis. SNP-carrying genes were classified accordingly to their functions (antigen presentation, skin barrier, innate immune responses and cytokine-dependent signalling).

Notes: REF>ALT, reference base > alteration base; dbSNP ID, database SNP identification number at NCBI; Genome position, UCSC Genome Browser hg19 assembly; rs, reference *SNP* ID number; Chr, chromosome; ERAP1, endoplasmic reticulum aminopeptidase 1; NFKBIZ, NF-κB inhibitor zeta; TRAF3IP2, TRAF3 interacting protein 2; TNFAIP3, TNF alpha induced protein 3; TYK2, tyrosine kinase 2; IL17RA, IL-17 receptor A, CDSN, corneodesmosin; CCHCR1, coiled-coil alpha-helical rod protein 1.

Notes: Genome position, UCSC Genome Browser hg19 assembly; REF/ALT, reference base / alteration base; SNP, single-nucleotide polymorphism; dbSNP ID, data base SNP identification number at NCBI; MAF, minor allele frequency from dbGaP in European population; Chr, Chromosome; rs, reference *SNP* ID number; ERAP1, endoplasmic reticulum aminopeptidase 1; HLA, Human Leukocyte Antigen; MICA, MHC class I polypeptide-related sequence A; HCP5, HLA complex P5; MICB-DT, MHC class I polypeptide-related sequence B- Divergent Transcription; LCE, late cornified envelope; CDSN, corneodesmosin; CCHCR1, coiled-coil alpha-helical rod protein 1; KLF4, Krüppel-Like Factor 4; IL, interleukin; IFIH1, Interferon Induced With Helicase C Domain 1; LTA, Lymphotoxin Alpha; DEFB, Defensin Beta; DDX58, DExD/H-Box Helicase 58; STAT2, signal transducer and activator of transcription 2; TYK2, tyrosine kinase 2; TNFRSF, Tumor necrosis factor receptor superfamily; RUNX, Runt-related transcription factor; NFKBIZ, NF-κB inhibitor zeta; TNIP1, TNFAIP3 Interacting Protein 1; MIR146A, MicroRNA 146a; TRAF3IP2, TRAF3 interacting protein 2; TNFAIP3, TNF alpha induced protein 3; TNFSF15, TNF superfamily member 15; SOCS1, suppressor of cytokine signaling 1; NOS2, Nitric Oxide Synthase 2; CARD14, Caspase Recruitment Domain Family Member 14; LD*, linkage disequilibrium;* MNV, Multi-nucleotide *variants*; INS, insertion. SNPs significantly associating with response to secukinumab are indicated in font bold.

Supplementary Table 3. Number of patients carrying SNPs associating with optimal response to secukinumab

SNP name	dbSNP ID	*n* Pz
HLA-Cw6	rs1131118	35
HLA-C_promoter1	rs13191343	43
HLA-C_promoter2	rs13207315	43
HLA-C_ promoter3	rs6900444	55
HLA-Cw6_LD1	rs12189871	35
HLA-Cw6_LD2	rs12191877	44
HLA-Cw6_LD3	rs4406273	35
HLA-Cw6_LD5	rs10484554	44
MICB-DT_v2	rs9267325	14
LTA_v1	rs1800683	16
LTA_v2	rs909253	16
DDX58_v1	rs34085293	14
TYK2_v3	rs2304255	15

dbSNP ID, database SNP identification number at NCBI; n Pz, number of patients

Supplementary Figure Legends

Supplementary Figure 1. Statistical values of association between rs13191343 and rs13207315 and response to secukinumab. Univariate logistic regression analysis evaluated the association between rs13191343 (HLA-C_promoter 1) and rs13207315 (HLA-C_promoter2) and clinical response to secukinumab, at the indicated weeks of treatment. The forest plot summarized the statistical values of regression analysis. The condition of good response to secukinumab is more likely to occur in the group of patients carrying the variant, as indicated by the odds ratio (OR) > 1. Squares in the *x*-axis indicate OR estimates for each observation point, and the error bars represent 95% confidence interval (CI). **p* value < 0.05 were considered significant and indicated in font bold.

Supplementary Figure 2. Association analysis between rs6900444 and clinical response to secukinumab treatment. Univariate logistic regression analysis evaluated the association between rs6900444 (HLA-C_promoter3) and clinical response to secukinumab, at the indicated weeks of treatment. Rs6900444-negative (SNP-NEG, gray line) patients reached a significant better response to secukinumab than positive patients (SNP-POS, dark gray line), in terms of achievement of PASI75 (A), PASI90 (B) and PASI100 (C). Regression analysis is also summarized in the forest plot in the lower panel. The condition of good response to secukinumab is more likely to occur in the group of patients carrying the variant, as indicated by the odds ratio (OR) > 1. Squares in the *x*-axis indicate OR estimates for each observation point, and the error bars represent 95% confidence interval (CI). **p* value < 0.05 were considered significant and indicated in font bold.

Supplementary Figure 3. Statistical values of association between rs1131118, rs12189871, rs4406273, rs12191877, and rs10484554 and response to secukinumab. Univariate logistic regression analysis evaluated the association between rs1131118 (HLA-Cw6), rs12189871 (HLA-Cw6_LD1), rs4406273 HLA-Cw6_LD3), rs12191877 HLA-Cw6_LD2), and rs10484554 (HLA-Cw6_LD5) and clinical response to secukinumab, at the indicated weeks of treatment. Statistical values of regression analysis are summarized in the forest plot (A) and (B). The condition of good response to secukinumab is more likely to occur in the group of patients carrying the variant, as indicated by the odds ratio (OR) > 1. Squares in the *x*-axis indicate OR estimates for each observation point, and the error bars represent 95% confidence interval (CI). **p* value < 0.05 were considered significant and indicated in font bold.

Supplementary Figure 4. Association analysis between rs1800683 or rs909253 and clinical response to secukinumab treatment. Univariate logistic regression analysis evaluated the association between rs1800683 (LTA_v1) or rs909253 (LTA_v2) variants and clinical response to secukinumab treatment, in terms of achievement of PASI75 (**A**), PASI90 (**B**) and PASI100 (**C**) responses. Regression analysis is also summarized in the forest plot in the lower panel. The condition of good response to secukinumab is more likely to occur in the group of patients not carrying the variant, as indicated by the odds ratio (OR) < 1. Squares in the *x*-axis indicate OR estimates for each observation point, and the error bars represent 95% confidence interval (CI). *p* value < 0.05 were considered significant (*) and indicated in font bold.