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Association between single nucleotide polymorphisms *IL17RA* rs4819554 and *IL17E* rs79877597 and Psoriasis in a Spanish cohort.

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ABSTRACT

Background: The *IL17* pathway plays an important role in the pathogenesis of psoriasis (PsO).
Objectives: To determine whether the variation at the *IL17* pathway genes was linked to the risk for PsO or had an effect on disease severity and the risk for Psoriatic arthritis (PsA).
Methods: Cross-sectional observational study of 580 psoriasis patients and 567 healthy controls who were genotyped for six single nucleotide polymorphisms (SNPs) in the *IL17RA* (rs4819554, rs879577), *IL17A* (rs7747909), *IL17F* (rs763780, rs2397084), and *IL17E* (rs79877597) genes.
Results: We found significant higher frequencies of *IL17RA* rs4819554 G carriers among the patients (OR = 1.33, 95%CI = 1.05–1.69; $p = 0.017$). The *IL17RA* rs4819554 G allele and *IL17F* rs2397084 TT genotype were significantly more frequent among Cw6 positive patients ($p = 0.037$ and $p = 0.010$, respectively). The *IL17E* rs79877597C allele was significantly more common among patients with severe forms of PsO ($p = 0.010$; OR = 2.42, 95%CI = 1.23–4.76), and the CC genotype with the presence of arthritis ($p = 0.032$; OR = 1.50, 95%CI = 1.04–2.18).
Conclusions: We identified the *IL17RA* rs4819554 SNP as a risk factor for PsO. The *IL17E* rs79877597 SNP was a modifier of the risk for PsO disease severity and PsA.

1. Introduction

Psoriasis (PsO) is a common, chronic inflammatory skin disease affecting approximately 2–4% of the population [1]. PsO is considered a multifactorial disease in which the genetic background interacts with environmental factors to define the individual's risk [2]. The genetic component affects not only the overall risk, but also the clinical type, age of disease onset, severity, or the risk for psoriatic arthritis (PsA) [3]. The first locus for PsO (*PSORS1*) was mapped to human chromosome 6p21.3, and further studies identified the Major Histocompatibilty Locus HLA_Cw6*0602 allele as the main PsO-risk factor [4]. In addition to this well characterized genetic association, other immunological relevant genes have been linked to the risk for PsO and pointed to new pathways implicated in this disease [5].

The IL-17 family comprises a group of cytokines with an active role on the acute and chronic immune responses [6]. This family consists of six members (IL-17A to F) and five receptors (IL-17RA to E) [7]. IL-17A is the founding member and defines a new subset of CD4+ effector T (Th17) cells. This cytokine induces the production of inflammatory mediators from epithelial and endothelial cells and fibroblasts [7,8]. It also mobilizes, recruits and activates neutrophils, thus connecting innate and adaptive immunity [9]. It has been shown that the cells that secrete IL-17 are present in psoriatic lesions in a higher number than in normal skin [10]. As well, increased levels of circulating IL-17-producing cells have been found in psoriatic patients, and higher levels of IL-17 were found in lesional skin and plasma of psoriatic patients compared to healthy individuals [10–12]. In PsO, both IL-17A and IL-17F have proinflammatory

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effects on keratinocytes and neutrophils. Keratinocytes express IL-17RA and respond to IL-17A and IL-17F producing, among others, IL-6, GM-CSF, AMPs and other chemokines that are positively regulated in PsO [1,12]. IL17E, also known as IL25, is mainly expressed by Th2 cells and is implicated in the production of Th2 cytokines and the subsequent recruitment of eosinophils [13,14]. IL17E also has inhibitory properties over Th17 cells [15].

Several common polymorphisms in the IL-17 family genes have been linked to the risk for developing autoimmune [16–18], inflammatory [8,19], or infectious [20,21] diseases, and even for susceptibility to several neoplasms [22,23]. To our knowledge there are few reports about the effect of the polymorphisms at *IL17/IL17RA* axis on the risk for developing PsO or PsA [24,25]. Thus, our main aim was to determine whether common DNA variants at *IL17RA*, *IL17A*, *IL17F* and *IL17E* genes were associated with the risk for developing PsO or have an effect on disease severity or the risk for PsA. The selection of the targeted single nucleotide polymorphisms (SNPs) was made after a carefully review of the existing literature (**Table A.1**).

2. Subjects and methods

2.1. Patients and controls

This was a cross-sectional and retrospective observational study including a total of 580 patients with chronic plaque PsO (mean age 47 ± 15 years; 54% men) and 567 controls (mean age 51 ± 14 years; 55% men). PsO patients were recruited through the Department of Dermatology of Hospital Universitario Central Asturias (HUCA) between January 2007 and August 2014. The control group consisted of non-related healthy individuals recruited through the Blood Bank and the Department of Dermatology of HUCA. All the participants were Caucasians from the region of Asturias (Northern Spain, total population 1 million), older than 18 years old, and gave their written informed consent to participate in the study. Ethics approval was also obtained by the Ethical Committee of HUCA. Patients' main demographic and clinical characteristics are summarized in Table 1. PsO was diagnosed based on clinical findings by two independent dermatologists, and the disease was defined as severe or non-severe according to the Psoriasis Area and Severity Index (PASI; severe, a PASI score ≥ 10). In all patients, PASI values were recorded previously to the onset of PsO therapy. The existence of arthritis was assessed by a rheumatologist according to Moll and Wright or more recent CASPAR criteria [26]. Demographic and clinical data including age of disease onset (early onset considered if the age of PsO onset was below or equal to 40 years), duration of PsO, nail involvement, familial history of PsO (familial PsO if there was at least one first- or second-degree affected relative) and other comorbidities different from PsA were also collected. All the patients had been previously genotyped for *HLA-Cw6* (PSORS1) [27].

Table 1
Main characteristics of the 580 patients with Psoriasis.

Main characteristics of the 580 patients with Psoriasis		
Gender (male/female)	313 (54%)/267 (46%)	
Age (years) (mean ± SD)	47.09 ± 14.66	
HLA-Cw6 presence	241 (42%)	
Family history of psoriasis*	297 (52%)	
Early onset psoriasis‡	427 (74%)	
	Age (median)	19
	HLA_Cw6 presence	208 (49%)
Late onset psoriasis‡	153 (26%)	
	Age (median)	52
	HLA_Cw6 presence	33 (22%)
Mild–to–moderate psoriasis#	287 (49%)	
Severe psoriasis#	293 (51%)	
Arthritis	170 (29%)	

PASI: Psoriasis Area and Severity Index; SD: standard deviation.
* The total number of patients in which the variable of family history of psoriasis was recorded was of 567 due to doubtful cases that could not be demonstrated.
‡ Early onset psoriasis: age ≤ 40 years; Late onset psoriasis: age > 40 years.
# Mild–to–moderate psoriasis: PASI < 10; Severe psoriasis: PASI ≥ 10.

2.2. SNPs genotyping

The selection of the SNPs was based on previous reports that described a positive association with diseases (**Table A.1).** The locations and predictive effects of the selected SNPs are shown in **Table A.2**.

SNPs were then determined in all the patients and controls trough Real Time Taqman assays (www.appliedbiosystems.com): rs4819554 and rs879577 in *IL17RA,* rs7747909 in *IL17A*, rs763780 and rs2397084 in *IL17F,* and rs79877597 in *IL17E*.

2.3. Statistical analysis

Statistical analysis was carried out using the R software system (version 3.0.2). The χ^2 test was used to compare genotype and allele frequencies between the groups and to determine the deviation of the genotype frequencies from the Hardy–Weinberg equilibrium. Odds ratios (OR) and their 95% confidence intervals (CI) were also calculated. The Student's *t* test was used to compare quantitative variables between the groups. We performed multivariate logistic regression analysis to adjust for risk factors. A $p < 0.05$ was considered as statistically significant.

3. Results

The observed genotype frequencies for the six SNPs did not deviate from the Hardy–Weinberg equilibrium in both, patients and controls. Minor allele frequencies (MAF) for the six genes in patients and controls are shown in Table 2. Only the *IL17RA* rs4819554 G showed significant differences between the two groups ($p = 0.017$).

We found significantly different allele and genotype frequencies for the *IL17RA* rs4819554, where G carriers (AG + GG) were significantly more common among PsO patients ($p = 0.017$), with an OR = 1.33 (95%CI = 1.05–1.69), with respect to the control group (Table 3). This SNP was also significantly associated with the Cw6 status: 48% of the Cw6-positive patients were G-carriers compared to 40% of G-carriers among the Cw6-negative patients ($p = 0.037$; OR = 1.43, 95%CI = 1.02–1.99) (Table 3). We did not find significantly differences between patients and controls for the *IL17RA* rs879557 allele/genotypes, but the rs879557 T-carriers were also more frequent among the Cw6-positive cases, although at a non-significant difference (**Table A.3**). A relation with Cw6 was also identified in the case of *IL17F* rs2397084 SNP, where PsO patients with the TT-genotype were more common among the Cw6-positive patients (OR = 2.07; 95%CI = 1.19–3.60; $p = 0.010$) (Table 4). Nevertheless, allele and genotype frequencies of these three above mentioned SNPs, *IL17RA* rs4819554, *IL17RA* rs879557, and *IL17F* rs2397084, did not differ between patients according to disease severity, presence of PsA, or other demographic or clinical characteristics (Tables 3–4**, Table A.3**.)

Additional significant differences were observed for the *IL17E* rs79877597 SNP (Table 5). Allele C carriers presented a more severe form of PsO ($p = 0.010$; OR = 2.42, 95%CI = 1.23–4.76). Also the CC genotype was a significant risk factor for PsA ($p = 0.032$; OR = 1.50, 95%CI = 1.04–2.18).

Regarding *IL17A* rs7747909 and *IL17F* rs763780 SNPs, no significant allele or genotype differences between patients with PsO and healthy controls were evidenced. In addition, no

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