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# Interleukin-12B (*IL-12B*) and Interleukin-23R (*IL-23R*) Gene Polymorphisms do not Confer Susceptibility to Psoriasis in a Southern European population: A Case-Control Study

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***Abstract*—Genome-wide association studies of psoriasis identified interleukin *(IL)-12B* and *IL-23R* as significantly associated loci with psoriasis, thus emphasizing to the important role of these genes in the pathogenesis of this disease and have influenced the development of medications that specifically target these key immunological players. Here we report an association study of a homogeneous Greek cohort from the island of Crete, consisting of 100 patients with PS and 195 controls, which were genotyped for rs3212227 and rs6887695 SNPs of the *IL-12B* and the rs7530511 and rs11209026 SNPs of *IL-23R* genes, respectively, using Taqman assays. Neither *IL12B* nor *IL23R* SNPs showed any association with psoriasis in the population under study. Apart from the previously reported evidence for the role of *IL-12B* and *IL-23R* in various populations, our results demonstrate no association of these gene polymorphisms with psoriasis in the Cretan population, thus highlighting the importance of comparative studies in different populations to confirm the previously detected genetic associations.**

***Index Terms*—gene polymorphism; *IL-12B*; *IL-23R*; psoriasis.**

## I. Introduction

Psoriasis (PS) (OMIM #177900) is a common, autoimmune, T-cell-mediated chronic inflammatory skin disease, affecting about 1.5–3% of Caucasians and less than 1.0% of Asians and Africans [1].The onset of disease usually occurs early in life (ages 15–30 years) and affects males and females equally. Moderate-to-severe cutaneous involvement can be burdening, as the condition can progress to cover a large body surface area including uncommon locations such as the hands and feet, genitals, and scalp, a situation that may even extend into generalized erythroderma.

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In histopathology, a mixed inflammatory infiltrate is found, mainly consisting of lymphocytes and monocytes [2].

Inflammatory processes induce the migration of interferon (IFN) γ-producing T-helper 1 (Th1) lymphocytes into the skin that play a key role in the pathogenesis of PS. Pathogenesis of PS is complex and, therefore, any of the involved factors such as immune cells, mediators (including cytokines and chemokines), genetic background, environmental conditions, gene–gene or gene–environment interactions may jointly influence the onset, manifestation, clinical course and disease outcome. About 20% to 30% of patients have associated psoriatic arthritis (PsA), a progressive, inflammatory arthropathy characterized by joint pain, swelling, and deformity, while its frequency vary widely according to the diagnostic criteria used in the study population [3].

Psoriasis is widely regarded as a multifactorial disease as its familial recurrence is well established [4]. In addition to the well-known *HLA-B* and *HLA-C* genes, solid evidence is available now for PS-risk variants of many genes from various pathways, such as *LCE* gene cluster [5], N-acetyltransferase 9 (*NAT9*), solute carrier family 9, isoform 3 regulatory factor (*SLC9A3R1*) and regulatory associated protein of MTOR (*RAPTOR*) at psoriasis susceptibility locus 2 (*PSORS2*) on chromosome 17q.25 as well as the primary disease locus (*PSORS1*), lying within the major histocompatibility complex (*MHC*) which contains the corneodesmosin gene (*CDSN*) [6]. Over the last years, genome-wide association studies (GWASs) have been a useful tool in the genetic dissection of PS, by identifying many loci as potential psoriasis susceptibility regions. Thus, additional detected candidate genes are mapping on at least nine non-MHC disease regions (*PSORS2-10*) [7] and the zinc finger protein 313 (*ZNF313*) locus [8], *TRAF3IP2* gene [9], E*RAP1* [10], a region on chromosome 13q13 harboring lipoma HMGIC fusion partner (*LHFP*) and component of oligomeric golgi complex 6 (*COG6*), a region on chromosome 15q21, several genes at *PSORS4* locus on chromosome 1q21 and a region of chromosome 4q27 [11]. Other promising candidate genes are interleukin 28 receptor-alpha (*IL28RA*), *REL*, Nitric oxide synthase 2 (*NOS2*), F-box and leucine-rich repeat protein 19 (*FBXL19*) (for details see [12] and [13], while Li et al. presented data suggesting that ADAM33, CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*) and Protein tyrosine

phosphatase, non-receptor type 22 (*PTPN22*) are true PS risk genes [14]. In addition, interaction studies between some of these genes have also been conducted so far [10].

Interleukin (IL)-12 and IL-23 are naturally occurring proteins that regulate specific components of the immune system. Both IL-12 and IL-23 have been associated with the pathogenesis of psoriasis, in part due to their relationship to the differentiation of naïve T-cells into Th (T-helper)1 and Th17 cells [15],[16]. Interestingly, IL-23 stimulates survival and proliferation of Th17 cells, a key cell type that regulates the production of other inflammatory cytokines (IL-17, IL-22, IL-21, IL-6, tumor necrosis factor (TNF-α) and is overproduced in dendritic cells and keratinocytes found in psoriatic plaques [17],[18]. *Interleukin-12B* and *IL23R* genes were the first definitive, non-HLA genetic risk factors identified for psoriasis, as shown in a GWAS conducted by Cargill et al. [19]. This study detected four non-HLA SNPs associated with psoriasis in a North American population. Two SNPs, rs3212227 (in the 3' untranslated region) and rs6887695 (upstream of the gene) were detected in the IL-12 beta gene (located chromosome 5q31.1–q33.1), which encodes the IL-12 beta-p40 subunit of the IL-12 and IL-23. Two additional PS-associated missense SNPs, rs7530511 (L310P) and rs11209026 (Q381R) were found in the IL-23 receptor gene (*IL-23R*), which is located on chromosome 1p31and also shares the IL-12b-p40 protein subunit. These associations have been confirmed further in a UK cohort by [20] and in another replication studies focused on the Chinese Han population [21] as well as in another Chinese population [5], thus concluding that both are key PS-susceptibility genes. Moreover, it has been suggested that certain genetic alteration of the IL-23 (p40 and p19) or IL-12 (p40 and p35) subunits as well as the IL-23 receptor or its ligand lead to enhanced IL-23 production and subsequent psoriasis susceptibility. However, other mutations that decrease the levels of IL-23 or IL-12 confer protection from psoriasis. Altogether, these findings indicate that genes participating in IL-12/23 signaling play a significant role in the pathogenesis of this disease [19],[22],[23].

Taking into account that a significant source of variability in the literature of autoimmune diseases has been the inability to replicate genetic findings across the major racial groups, the aim of this study is to investigate whether the two polymorphisms from each of the *IL-12B* and *IL-23R* genes also play a role in psoriasis susceptibility in the genetic homogeneous population of the island of Crete.

## II. Materials and Methods

### A. Study population

The study group comprises of 195 healthy subjects and 100patients with PS from unrelated families living in Crete. Age - and sex - matched healthy volunteers from the Department of Transfusion Medicine of the University Hospital of Crete served as controls. All PS patients were seen by an experienced dermatologist (S. K-K) from the Department of Dermatology of the University Hospital of Crete. Patients with psoriatic arthritis (PsA) (N=39) were also evaluated by rheumatologist. All patients and controls were included if they were of Cretan origin and had no other autoimmune diseases. Control patients had a negative family history of PS or PsA. Ethnic bias within the population studied was minimized by excluding patients that were not of Cretan origin (defined as having the four grandparents of Cretan ancestry). The study was performed in the Laboratory of Dermatology, Faculty of Medicine, University of Crete after obtaining approval of the institutional committee and informed consent of patients or guardians.

### B. Genetic analysis of IL-12B and IL-23R polymorphisms

Whole blood was collected in EDTA-containing tubes and genomic DNA was isolated from blood leucocytes by using the commercial kit Qiamp DNA Blood Mini kit (QIAGEN Inc, CA, USA). The extracted DNA was stored at -20$^{o}$C until to be used for the genotyping. The rs6887695 and rs3212227 SNPs in *IL-12B* as well as the rs11209026 and rs7530511 SNPs in *IL-23R* genes were genotyped via TaqMan 5'allelic discrimination technology using predesigned SNPs genotyping assays provided by Applied Biosystems (Foster City, California, USA) (TaqMan assay numbers C_1994992_10, C_2084293_10, C_1272298_10, C_2990018_10, respectively). Genotypes were scored blindly and analysis of all ambiguous samples was repeated.

### C. Statistical analysis

In the case-control comparisons, only unrelated cases and controls were used. The *IL-12B* and *IL-23R* gene variants under investigation were evaluated for deviation from Hardy–Weinberg equilibrium (HWE) by comparing observed and expected genotype frequencies by means of $x^2$ Fisher's exact test in the control groups. Logistic regression adjusted by sex and age were used to examine the association between the genetic variant and the case–control status. As one polymorphism was investigated for each gene, a p value of 0.05 was defined as significant.

## III. Results

The PS study group (n=100) consisted of 51 (51%) men and 49 (49%) women. The unrelated healthy controls (n=195) were of similar age and sex. Mean (±SD) age in patients was 49.38 ± 15.2 years and in controls 40.35 ± 8.96 years. Twenty two patients with type I (early onset) and 88 with type II (late onset) psoriasis were involved in this study. Allele (200 cases and 390 controls) and genotype frequencies of the analyzed samples of the IL-12B and IL-23R polymorphisms are depicted in Table 1. All the markers conformed to the expected HWE proportions. The patients with PS did not present any genotypic or allelic frequencies more frequently than in controls. Assuming the odds ratio observed in this study and prior analyses, the power of these analyses for both *IL-12B* and *IL-23R* polymorphisms was less than 0.10 using a type I error probability of 0.05. Furthermore, haplotypes were evaluated but not significant results were observed (data not shown).

The analysis conducted by sex did not detect any sex-dependent significant difference with regard to the *IL-12B* and *IL-23R* genotypes and the development of PS (data not shown). Moreover, when subjects stratified according to the age no association was detected regarding either the genotypic or allelic frequencies. Comparison of controls and different psoriasis subgroups stratified according

to the age of onset did not confirm any association of the risk alleles of the SNPs under investigation with age of onset of disease either at age of onset ≤ 20 (Type I) or > 20 (Type II) (data not shown).

Comorbidities of PS include PsA, a seronegative inflammatory joint disorder distinct from RA. Taking into account that recent reports have confirmed association SNPs mapping *IL-23R* and *IL-12B* genes with psoriasis susceptibility, a task of this study was to determine whether these variants are also associated with susceptibility to psoriatic arthritis (PsA). Thus, it was of great importance to explore the putative association between the SNPs under investigation and PsA. The presence of arthritis does not increase the association of the polymorphisms with PS as shown by comparing the genotype or allele frequencies in 39 PS patients with PsA versus controls (data not shown). The former finding is further strengthened upon comparison of the allele frequencies of controls with a subgroup of PS patients without arthritis, thus confirming the lack of association between both polymorphisms under study and PSA (detailed tables are not shown).

Interestingly, it was calculated that by adding 100 PS and /or 100 PsA cases, a task that is actually impossible at the moment considering the size of the Cretan population, the power remains low and the chance of getting statistically significant results is still low. We would need a study with approximately 2000 cases and 1000 controls to be able to identify the observed effects with a probability of 0.80 with a type I error probability of 0.05.

**Table 1. Genetic association of four SNPs with PS analyzed in 100 psoriasis patients and 195 controls from Greece**

| Marker | Gene | Number | | MAF | | Genotype counts | | p | OR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | | Cases | Controls | Cases | Controls | Cases | Controls | | |
| rs3212227 | *IL-12B* | 100 | 195 | 0.255 | 0.285 | 57/35/8 | 99/81/15 | 0.66 | 0.91 (0.6-1.38) |
| rs6887695 | *IL-12B* | 100 | 195 | 0.335 | 0.392 | 40/49/11 | 68/101/26 | 0.32 | 0.82 (0.55-1.21) |
| rs7530511 | *IL-23R* | 100 | 195 | 0.110 | 0.146 | 81/16/3 | 143/48/4 | 0.42 | 0.8 (0.45-1.36) |
| rs11209026 | *IL-23R* | 100 | 195 | 0.072 | 0.085 | 87/13/0 | 169/24/2 | 0.7 | 1.14 (0.57-2.22) |

MAF, Minor Allele Frequency; OR, odds ratio; CI, confidence interval

## IV. Discussion

In this case-control association study, we failed to confirm the positive association of *IL-12B* and *IL-23R* variants with psoriasis in a Greek population, in contrast to all previous reports for significant associations of these variants with the susceptibility for PS [3],[10]. This might be attributed to the different genetic background of the different ethnic groups, resulting in a lower incidence rate in the Greek population. Notably, such a high level of reproducibility of gene predisposition toward a complex immune disease in all the other populations but Cretan is quite unusual and strongly suggests that the *IL-12B* and *IL-23R* gene plays a key role in psoriasis [21].

A role for IL12B and IL23R in pathogenesis of psoriasis has already been demonstrated by substantial biological and clinical evidence. Of particular interest and functional importance related to the genetic finding is the observation that increased IL12B expression is observed in psoriatic skin lesions, which could be modulated by the non-coding, disease-associated SNPs; indeed, rs3212227 SNP appeared to be a functional SNP affecting IL12B expression in what appears to be cell-type-dependent fashion [24],[25],[26],[27]. Of note, IL-12/23 has also been implicated in the pathophysiology of Crohn's disease; however the complex relationship between Th1 and Th17 cells has not been completely analyzed yet [28]. It was thought that IL-23 may play important roles in controlling the differential of Th1/Th17 balance in both ulcerative colitis and Crohn's disease, although Th17 cells seem to exist in both diseases [29]. Furthermore, IL-12/23 have been strongly implicated in the pathogenesis of multiple sclerosis [30], while patients deficient in IL-12/23 or defects of their pathway receptors have shown susceptibility to infections such as Mycobacterium or Salmonella. Notably, the R381Q polymorphism of IL23R is also associated with Ankylosing Spondylitis (AS) [31], while the A allele of rs3212227 SNP of *IL-12B* has been associated with type 1 diabetes [32]. Both IL-12 and IL-23 have been proposed as targets for the treatment of psoriasis and new therapies, including a monoclonal antibody against a subunit shared by IL-12 and IL-23, have been developed to treat psoriasis [33].

Our data failed to detect a link between the polymorphism under study and PsA. Of note, PsA was not correlated with the *PTPN22*, *STAT4*, *CD40* and *NCOA5* gene polymorphisms that were analyzed recently in the same Cretan cohort [34],[35]. Obviously, this could be a result of the low power of the study due to the small size of the sub-groups examined. Notably, the effects observed are similar to those reported in previous articles, suggesting that main problem for the lack of reproducibility is statistical power.

In conclusion, our study did not confirmed the significant association between PS and both *IL-12B* and *IL-23R* loci in a Greek population. How these SNPs, which seem most likely to be functionally important according to previous studies conducted in various ethnic and racial populations, were not found to be associated with PS in our population, is an issue that remains to be tested. It is worth noting that inconsistencies observed recently in European derived and Cretan cohorts, with regard to genetic associations between various autoimmune diseases and susceptibility genes, i.e. RA and *PTPN22*, SLE and *STAT4*, probably due to the genetic peculiarities of the Cretan population and, thus, pinpointing probably the importance the present findings whilst the limited size of the cohort examined. Crete is the largest island of Greece, with about 0.65 million inhabitants and its population offers advantages for genetic association studies, since its members share the same genetic and cultural background and a common environment. All these factors enable genetic studies, given that the validity of genetic association studies is greatly affected by genetic heterogeneity, the low penetrance of individual disease alleles, and the potential for gene–gene and gene–environment interactions [36]. Obviously, the major weakness of our study deals with the limited sample size and our research needs to be extended to a higher number of patients and controls.

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