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ORIGINAL ARTICLE

ERAP1 and *ERAP2* Gene Variations Influence the Risk of Psoriatic Arthritis in Romanian Population

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Abstract Psoriatic arthritis (PsA) is a chronic inflammatory disorder that belongs to the group of spondyloarthritis (SpA). It was found that single nucleotide polymorphisms (SNPs) of endoplasmic reticulum aminopeptidase (*ERAP1* and *ERAP2*) genes influence the risk of ankylosing spondylitis, the most common form of SpA and the risk of psoriasis. Our purpose was to investigate the possible association of *ERAP1* and *ERAP2* gene SNPs with psoriatic arthritis susceptibility in Romanian population. Subsequent analyses included patients' subgroups according to HLA-B27 status. Psoriatic arthritis patients ($N = 98$) and random healthy controls ($N = 139$) were genotyped for *ERAP1/2* genes SNPs rs30187, rs27044, rs2910686, and rs2248374 by TaqMan Allelic Discrimination Assays. An additional control group ($N = 108$; 100% HLA-B27 positive) was used for subsequent analyses. The results showed the association of rs2248374 SNP of *ERAP2* gene with the risk of PsA, especially for HLA-B27 negative disease ($p = 0.02$; OR 1.59). *ERAP2* haplotype GT (rs2248374/rs2910686) was significantly under-represented in PsA patients than in controls (43 vs. 55%; $p = 0.02$). The analysis of *ERAP1* SNPs in HLA-B27 positive controls and PsA subgroup showed strong evidence of association for rs30187 ($p = 0.005$; OR 2.73) and for CC rs30187/rs27044 haplotype (47% in patients vs. 70.5% in controls; $p = 0.006$). In conclusion, we found a significant association of *ERAP2* with PsA and HLA-B27 negative PsA, while *ERAP1* association was restricted only to HLA-B27 positive disease. To our knowledge, this is the first study that investigated *ERAP2* polymorphisms in relation to PsA susceptibility.

Keywords Psoriatic arthritis · ERAP1 · ERAP2 · Single nucleotide polymorphism · Haplotype

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Introduction

Psoriatic arthritis (PsA) is defined as a chronic rheumatic disease characterized by psoriatic skin lesions and inflammation of peripheral and/or axial joints. The PsA prevalence was estimated between 0.10 and 0.25% in the general population (Lee et al. 2010). PsA patients often have associated comorbidities like hypertension, cardiovascular disease, obesity, depression, and anxiety that imply a low quality of life (Palmer et al. 2016). Data regarding the complex pathophysiological mechanisms of PsA are still limited, and despite the availability of biological therapies, there is no cure for this disorder. Therefore, a great amount of research is carried out to

elucidate the immunogenetic pathways of the disease and to facilitate the way for the discovery of new treatments.

Several gene families were implicated in the pathology of PsA-related conditions such as psoriasis and ankylosing spondylitis: *IL12/23*, *LCE*, *ERAP* (Cortes et al. 2013; Harden et al. 2015; Kenna et al. 2015; O'Rielly and Rahman 2014), but limited knowledge is available regarding psoriatic arthritis, some of the reasons being the reduced number of patients compared with other immune-related diseases and the greater clinical heterogeneity of the disease itself (O'Rielly and Rahman 2014).

Endoplasmic reticulum aminopeptidases 1 and 2 (ERAP1 and 2) are zinc-dependent multifunctional enzymes that recognize and process a vast variety of antigenic peptides to generate epitopes for presentation by MHC class I molecules (Mpakali et al. 2015) and are implicated in the regulation of blood pressure (Cifaldi et al. 2012; Kim et al. 2015). ERAP1 is involved also in postnatal angiogenesis and in proinflammatory cytokine receptor shedding (Cifaldi et al. 2012). Both *ERAP* genes are highly polymorphic, with several nonsynonymous polymorphisms (functional variants) that affect the enzymatic functions of ERAP1 and 2 proteins (Reeves et al. 2014). Recent studies have shown the association of *ERAP1* and *ERAP2* variants with ankylosing spondylitis and psoriasis (Kenna et al. 2015; Reeves et al. 2014; Yin et al. 2015). As regarding psoriatic arthritis, only a few studies have addressed the association with *ERAP1* gene variations (Jadon et al. 2013; Yang et al. 2013). The search of the literature revealed no data about *ERAP2* gene and PsA.

Our purpose was to investigate the possible association of *ERAP1* and *ERAP2* gene single nucleotide polymorphisms (SNPs) with psoriatic arthritis susceptibility in Romanian population.

Materials and Methods

Study Population and Ethics

A total number of 345 unrelated Caucasian individuals of Romanian origin were included in the study. Psoriatic arthritis patients ($N = 98$; male/female: 42/56; median age: 52 years) were recruited from the Department of Rheumatology, "I. Cantacuzino" Hospital, Bucharest, Romania. PsA patients were diagnosed according to the Classification criteria for Psoriatic Arthritis by an experienced rheumatologist (dr. M. Bojinca). Patients were classified at the time of study entry as having oligoarticular PsA (2–4 joints involved, 26 patients), polyarticular PsA ($\geq$5 joints involved, 40 patients) or axial disease (a history of inflammatory back pain and radiographic evidence of sacroiliitis or spondylitis, 32 patients). Psoriasis onset before 40 years of age (type I psoriasis) was recorded in 39 patients (40%).

The controls were potential organ donors with no history of a diagnosed rheumatic condition, psoriasis or inflammatory bowel disease. We used a total number of 247 controls separated in two groups: a group of 139 random healthy controls (male/female: 71/68; median age: 36 years) and a group of 108 healthy controls, all HLA-B27-positive (male/female: 50/58; median age: 33 years).

The study was approved by the Ethic Committee of "I.C. Cantacuzino" Hospital, Bucharest, Romania. The details were explained to all patients and controls and consent for genetic screening was obtained. The study was performed in accordance with the principles stated in the Declaration of Helsinki and its later revisions.

SNP Selection and Genotyping

Based on previous findings from our laboratory and from the literature (Cherciu et al. 2013; Robinson et al. 2015), we selected for this study two functional polymorphisms for *ERAP1* gene: rs30187 (Lys528Arg) and rs27044 (Gln730Glu). These coding SNPs influence ERAP1's enzymatic activity, therefore affecting the quantity of the antigen-specific peptides which are processed (Evnouchidou et al. 2011). For *ERAP2* gene, beside the intronic SNP rs2910686 (Cortes et al. 2013), we chose rs2248374 that causes a functional ERAP2 protein knockout, because the G allele determines a loss of ERAP2 protein expression (Andres et al. 2010).

Genomic DNA was obtained from EDTA-treated peripheral blood samples using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to manufacturer protocol.

The SNPs genotyping was performed by real-time polymerase chain reaction (PCR) with TaqMan Allelic Discrimination Assays (C_3056885_10, C_3056870_10, C_25649529_10 and C_26382310_10, 7300 Real-time PCR System, Applied Biosystems, Foster City, CA). HLA-B27 typing was carried out as previously described (Popa et al. 2010).

Statistical Analysis

Allelic and genotypic frequencies were compared between PsA cases and controls, and odds ratio (ORs) and adherence to the Hardy–Weinberg equilibrium (HWE) were calculated using the PLINK v 1.07 software (Purcell et al. 2007). Additional tests for genotypes association were performed with DeFinetti program (http://ihg2.helmholtzmuenchen.de/cgi-bin/hw/hwa1.pl) (Strom and Wienker 2016).

For haplotype construction, genotype data from cases and controls were used to estimate intermarker linkage disequilibrium (LD) by calculating pairwise r^2 with Plink 1.07. The estimation of haplotype frequencies and association tests were performed using Plink 1.07 software.

Results

The control and patient groups showed no departure from HWE for all studied SNPs

The alleles' frequency and the distribution of genotypes of tested polymorphisms in the PsA group and random healthy controls are shown in Table 1. For *ERAP2* gene, the minor allele A of rs2248374 was overrepresented in patients versus controls ($p = 0.04$; OR 1.45). The carriers of this allele (AA and AG genotypes) have an increased risk for the disease (81 vs. 69%; $p = 0.02$; OR 1.99). These data point to the fact that rs2248374 G variant, which abolishes ERAP2 protein expression, is a protective factor for PsA. For rs2910686, the carriers of the major allele (TT and CT genotypes) were significantly more frequent in controls than in patients (87.7 vs. 77.3%; $p = 0.03$; OR 0.47). We found no association of *ERAP1* SNPs with the risk of PsA.

Due to their contiguous physical location on chromosome 5q15 (Tanioka et al. 2003), we performed intra- and inter-genic correlations for *ERAP1* and *ERAP2* SNPs. The r^2 values showed a moderate level of intra-genic LD in our population ($r^2 = 0.54$ for *ERAP1* SNPs and $r^2 = 0.67$ for *ERAP2* SNPs) and no LD between the two genes. Three four-marker haplotypes had frequencies over 5% in controls and patients. Of these, the haplotype CCGT (rs27044/rs30187/rs2248374/rs2910686) was significantly underrepresented in PsA patients (25 vs. 34.5% in controls, $p = 0.02$), but the omnibus test for this analysis did not reach statistical significance ($p = 0.25$).

Psoriatic arthritis belongs to the group of seronegative spondyloarthritis together with ankylosing spondylitis (AS). It is well documented the association of HLA-B27 with AS, but also with PsA (Popa et al. 2010). Recent studies described the association of *ERAP2* SNPs with HLA-B27 negative AS (Robinson et al. 2015). Therefore, we performed an analysis of HLA-B27 negative controls ($N = 117$) and PsA patients ($N = 78$) in our study. Associations were observed for both *ERAP2* SNPs at allele and genotypic level (Table 2). For rs2248374, the results show that the subjects carrying the GG genotype (no ERAP2 protein expression) were more frequent in the control group (31.6 vs. 18% in patients), while the individuals carrying the AA genotype (complete ERAP2 protein expression) were overrepresented in patients (30.7 vs. 21.3% in controls). The association was significant ($p = 0.02$; OR 0.39; 95% CI 0.17–0.90). Two haplotype combinations (rs2248374/rs2910686) were associated with PsA: AC with increased risk (47% in PsA vs. 36% in controls; $p = 0.03$) and GT with protection against the disease (43% in PsA vs. 55% in controls; $p = 0.02$). A marginal omnibus association was obtained for this analysis ($p = 0.05$; Supplementary Table 1). No association was found with *ERAP1* gene variants for the HLA-B27 negative group.

Next, we were interested in checking the association of *ERAP1* gene SNPs with HLA-B27 positive PsA. Previous findings from the literature and from our laboratory describe the association of *ERAP1* with HLA-B27 positive AS (Evans et al. 2011) and with HLA-B27 positive spondyloarthritis (Cherciu et al. 2013). For this analysis, we used a HLA-B27 positive control group ($N = 108$) for which genotyping data for *ERAP1* SNPs were available from our previous study (Cherciu et al. 2013). Although the subgroup of patients was small ($N = 20$), a strong association was obtained for rs30187 (Table 3). The frequency of the minor allele T was 29% in controls and 53% in patients ($p = 0.005$; OR 2.73; 95% CI 1.311–5.695). The carriers of the minor allele (CT and TT genotypes) were significantly more frequent in patients than in controls (76.4 vs. 47.2%; $p = 0.02$; OR 3.63, 95% CI 1.113–11.852). The haplotypes analysis showed a significant omnibus test as a result of the association of CC rs30187/rs27044 combination with protection to PsA (47% in patients vs. 70.5% in controls; $p = 0.006$), while TG haplotype was a risk factor for the disease (41% in patients vs. 23.8% in controls; $p = 0.03$; Supplementary Table 2). Due to the small number of subjects available for this subgroup of patients, these results need further confirmation on larger cohorts from our population.

Discussion

We performed a case–control study regarding the association of particular genetic variants of *ERAP1* and *ERAP2* genes with psoriatic arthritis in Romanian population. Subsequent analyses included patients' subgroups according to HLA-B27 status. To our knowledge, this is the first study that investigated *ERAP2* polymorphisms in relation to PsA susceptibility.

Recently, a number of genome-wide association studies identified non-HLA (human leukocyte antigen) susceptibility loci for psoriasis in Caucasian and Asian populations (Yin et al. 2015). Among these, *ERAP1* gene was repeatedly confirmed as a genetic factor implicated in psoriasis pathogenesis (Strange et al. 2010; Tsoi et al. 2012). One study found the association of *ERAP2* SNP rs2910686 and

Table 1 Results of the association study of *ERAP1* and *ERAP2* single nucleotide polymorphisms (SNPs) and PsA

SNP	Controls[a], *N* (%)	PsA, *N* (%)	Statistics
ERAP1			
rs30187			
Minor allele			
T	89 (32)	69 (39.2)	OR 1.37
			95% CI 0.92–2.03
			$p = 0.11$
Genotype			
TT + CT	15 + 59 (53.2)	12 + 45 (64.8)	OR 1.61
CC	65 (46.8)	31 (35.2)	95% CI 0.93–2.79
			$p = 0.08$
rs27044			
Minor allele			
G	64 (23)	58 (29.6)	OR 1.40
			95% CI 0.92–2.12
			$p = 0.10$
Genotype			
GG + CG	7 + 50 (41)	9 + 40 (50)	OR 1.43
CC	82 (59)	49 (50)	95% CI 0.85–2.42
			$p = 0.17$
ERAP2			
rs2248374			
Minor allele			
A	127 (45.6)	108 (55)	OR 1.45
			95% CI 1.01–2.10
			$p = 0.04$
Genotype			
AA + AG	31 + 65 (69)	28 + 52 (81.6)	OR 1.99
GG	43 (31)	18 (18.4)	95% CI 1.06–3.72
			$p = 0.02$
rs2910686			
Minor allele			
C	104 (37.4)	89 (45.8)	OR 1.41
			95% CI 0.97–2.05
			$p = 0.06$
Genotype			
TT + CT	52 + 70 (87.8)	30 + 45 (77.3)	OR 0.47
CC	17 (12.2)	22 (22.7)	95% CI 0.23–0.95
			$p = 0.03$

p values <0.05 are indicated in bold

PsA psoriatic arthritis, *OR* odds ratio, *CI* 95% confidence interval

[a] Frequencies of *ERAP1* polymorphisms in controls were described previously by Cherciu et al. (2013)

psoriasis susceptibility (Tsoi et al. 2012). Yin et al. (2015) concluded that several genetic factors have population-specific effects that contribute significantly to the ethnic diversity of psoriasis prevalence.

Like psoriasis, psoriatic arthritis has a complex genetic background and some authors consider that it has an even higher genetic heritage than psoriasis (Stuart et al. 2015; Yang et al. 2013). On the other hand, psoriatic arthritis shares genetic similarities with the spondyloarthritis group of diseases, mainly ankylosing spondylitis, for which *ERAP1* and *2* have been identified as genetic risk factors (Robinson et al. 2015). There are no studies in Romanian population regarding the association of *ERAP* genes with psoriatic arthritis. We investigated two nonsynonymous

Table 2 Results of the association study of *ERAP2* single nucleotide polymorphisms (SNPs) and PsA in HLA-B27 negative individuals

SNP	HLA-B27 negative controls, *N* (%)	HLA-B27 negative PsA, *N* (%)	Statistics
ERAP2			
rs2248374			
Minor allele			
A	105 (44.8)	88 (56.4)	OR 1.59
			95% CI 1.05–2.39
			***p* = 0.02**
Genotype			
AA + AG	25 + 55 (68.4)	24 + 40 (82)	OR 2.11
GG	37 (31.6)	14 (18)	95% CI 1.05–4.24
			***p* = 0.03**
rs2910686			
Minor allele			
C	85 (36.3)	73 (47.4)	OR 1.58
			95% CI 1.04–2.38
			***p* = 0.02**
Genotype			
TT + CT	45 + 59 (88.9)	22 + 37 (76.7)	OR 0.41
CC	13 (11.1)	18 (23.3)	95% CI 0.18–0.89
			***p* = 0.02**

p values <0.05 are indicated in bold

PsA psoriatic arthritis, *OR* odds ratio, *CI* 95% confidence interval

polymorphisms of *ERAP1* gene and two from *ERAP2* gene, one of them causing no ERAP2 protein expression, in relation with PsA susceptibility in Romanians.

We describe for the first time the association of *ERAP2* variants with PsA, the association being stronger for HLA-B27 negative subjects. The G allele of rs2248374 causes a truncated ERAP2 mRNA that is degraded by nonsense-mediated decay, thus influencing the levels of MHC class I expressed on the surface of B cells and the immune response (Andres et al. 2010). Our results show that PsA patients have a significant much higher frequency of A allele of rs2248374 (which means ERAP2 protein expression).

Studies from large patient cohorts found that in AS this SNP was associated with HLA-B27 negative disease, similar to our results, but also with HLA-B27 positive AS when the analysis was controlling for *ERAP1* associations (Robinson et al. 2015). Since we did not find an association of *ERAP1* with the whole PsA group and the HLA-B27 subgroup was very small, we did not perform this analysis.

The most important outcome of these results resides in the clinical management of the patients. ERAP inhibition may offer a novel therapeutic strategy for PsA given that aminopeptidase inhibitors are currently in development (Zervoudi et al. 2013). PsA patients that express ERAP2 could benefit from ERAP2 inhibition.

Regarding the association between *ERAP1* coding SNPs and the susceptibility to PsA, there are several studies that addressed this issue. Jadon and collaborators did not find any association between rs30187 and PsA, including HLA-B27 positive patients, but this analysis was not done using an HLA-B27 positive control group as in our study (Jadon et al. 2013). A study on a Chinese population reported a significant association of *ERAP1* SNP rs27524 and PsA (Yang et al. 2013), while a large case–control study conducted on the Spanish population did not find any association between *ERAP1* rs27524 and PsA (Julia et al. 2012). These results could be explained by ethnic variations, heterogeneity of the disease and also by ERAP1 function itself. As ERAP1 plays an important role in MHC class I peptide processing, different studies supported the idea that *ERAP1* variants only influence diseases susceptibility in individuals carrying certain HLA alleles, for example the *HLA-C* risk allele in psoriasis and HLA-B27 in AS (Evans et al. 2011; Strange et al. 2010). Our previous study on spondyloarthritis patients (Cherciu et al. 2013) and the present one provide evidence that sustain this HLA-related association.

The main limitation of the present study is the reduced number of patients and controls. Future studies on larger groups of patients and controls from different populations may help confirm our findings and elucidate the contribution of *ERAP1/2* to the ethiopathogenesis of psoriatic arthritis and related conditions.

In conclusion, we found a significant association of *ERAP2* with PsA and HLA-B27 negative PsA, while

Table 3 Results of the association study of *ERAP1* single nucleotide polymorphisms (SNPs) and PsA in HLA-B27 positive individuals

SNP	HLA-B27 positive Controls[a], *N* (%)	HLA-B27 positive PsA, *N* (%)	Statistics
ERAP1			
rs30187			
Minor allele			
T	63 (29.2)	18 (52.9)	OR 2.73
			95% CI 1.31–5.69
			***p* = 0.005**
Genotype			
TT + CT	12 + 39 (47.2)	5 + 8 (76.5)	OR 3.63
CC	57 (52.8)	4 (23.5)	95% CI 1.11–11.85
			***p* = 0.02**
rs27044			
Minor allele			
G	53 (24.5)	16 (40)	OR 2.05
			95% CI 1.01–4.14
			***p* = 0.04**
Genotype			
GG + CG	8 + 37 (41.7)	4 + 8 (60)	OR 2.10
CC	63 (58.3)	8 (40)	95% CI 0.79–5.55
			$p = 0.12$

p values <0.05 are indicated in bold

PsA psoriatic arthritis, *OR* odds ratio, *CI* 95% confidence interval

[a] Frequencies of *ERAP1* polymorphisms in controls were described previously by Cherciu et al. (2013)

ERAP1 association was restricted only to HLA-B27 positive disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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