

The association of HLA-C and ERAP1 polymorphisms in early and late onset psoriasis and psoriatic arthritis patients of Hungary

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Abstract

Introduction: Single nucleotide polymorphisms (SNPs) of the HLA-C and ERAP1 genes were recently determined to contribute to psoriasis susceptibility. However, data regarding the association of these genes with specific sub-groups of psoriasis are scarce.

Aim: To examine the possible association of the HLA-C and ERAP-1 polymorphisms with early and late onset psoriasis and psoriatic arthritis.

Material and methods: Five ERAP1 SNPs and two HLA-C SNPs were genotyped in 105 psoriatic arthritis patients, 214 cutaneous psoriasis patients and 200 healthy individuals. Haplotypes were constructed for three ERAP1 SNPs (rs17482078, rs10050860, rs30187), and interaction between HLA-Cw*0602 and ERAP1 was also analysed.

Results: The HLA-Cw*0602 rs10484554 SNP was found to be a strong susceptibility factor for early onset cutaneous psoriasis and early onset psoriatic arthritis. ERAP1 SNPs (rs10050860, rs17482078, rs27525) appear to have a protective function for early onset psoriatic arthritis. The haplotype B was identified as a susceptibility factor for late onset psoriatic arthritis. In HLA-C positive individuals the rs27524 ERAP1 SNP was associated with a significantly increased risk of psoriatic arthritis development, whereas the rs27525 ERAP1 SNP had the opposite effect.

Conclusions: These results suggest that the HLA-C and ERAP1 genes contribute to the pathogenesis of psoriasis and psoriatic arthritis in an age-dependent manner.

Key words: HLA-C, ERAP1, psoriasis, psoriatic arthritis, polymorphism.

Introduction

Psoriasis is a common, chronic immune-mediated skin disease. Clinically, psoriasis is characterized by the presence of well-demarcated, scaly, erythematous skin lesions, and is frequently associated with arthritis [1]. Psoriatic arthritis is a seronegative inflammatory arthritis present in nearly 25% of patients with psoriasis and develops after an average interval of about one decade [2]. Psoriatic arthritis is defined as a subtype of spondyloarthropathies, based on common human leukocyte antigen (HLA) associations. Clinically, this disease is characterized

by changing degrees of oligoarthritis, polyarthritis and spondylitis and typically involves dactylitis, distal interphalangeal joint involvement or mutilating arthritis [2, 3].

Early onset psoriasis, or type I psoriasis, refers to patients with an onset before 40 years of age, more serious disease course than the late onset psoriasis, strong family history, and HLA-C*06 positivity. Early onset psoriasis has been reported in 75% of patients with psoriasis; hence, it affects the majority of patients with psoriasis. Late onset psoriasis, or type II psoriasis, in contrast, is characterized by an onset at or after 40 years, less severe clinical symptoms and rare family inheritance [4, 5].

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Recently, age at disease onset (with a cut-off value at 40 years) has been found similarly important in the characterization of the disease phenotype in psoriatic arthritis as well [6].

Single nucleotide polymorphisms (SNPs) of several genes have been identified as contributing to psoriasis susceptibility [7, 8]. We and others have previously reported a significant association with variants of the *HLA-Cw*0602*, *IL23R*, *LCE3C*, *LCE3B-del* [9, 10], *IL12R*, *IL23* [11], *TNFSF15* [3], and *ERAP1* genes [12–14]. Psoriatic arthritis is strongly associated with the *HLA-B13*, *HLA-B57*, *HLA-B39*, *HLA-Cw6* and *HLA-Cw7* alleles [8]. While psoriatic arthritis tends to have a more severe disease course and appears earlier in *HLA-B*27* positive patients, the latency between the onset of psoriasis and onset of joint symptoms is longer in *HLA-Cw*0602* positive patients [6, 15].

Genetic variants of the *endoplasmic reticulum-associated amino-peptidase 1 (ERAP1)* gene has recently been reported to be associated with ankylosing spondylitis (AS), psoriasis [16], and Behcet's disease [17]. The ERAP1 protein belongs to the M1 family of zinc metallopeptidase enzymes and is encoded by a gene on chromosome 5q15 [18]. ERAP1 trims peptides imported into the endoplasmic reticulum at their N-terminus and contributes to the shaping of the antigenic repertoire presented by class I major histocompatibility complex (MHC) molecules [19]. Depending on the peptide length and sequence composition, ERAP1 has the ability to both destroy and create peptide cargos for MHC class I molecules [20]. The ERAP1 protein also contributes to the shedding of the membrane-bound receptors of inflammatory cytokines, such as IL-1R2, TNFR1 and IL-6R [21]. ERAP1 likely plays a pivotal role in the protection from infectious diseases by contributing to the maintenance of immune tolerance and control of inflammation [22]. The association of *ERAP1* variants with psoriasis has been investigated recently in populations of European and Chinese ancestry. Two *ERAP1* variants, rs27524 (noncoding) and rs30187 (Lys528ARG), were found to be genome-wide risk factors for psoriasis [12]. Furthermore, dominant epistasis between *HLA-Cw*0602* and the *ERAP1* rs30187 SNP was identified in studies [12–14]. Another recent work identified the *ERAP1* rs27432 SNP (intronic) as a variant strongly associated with psoriasis [23]. In Han Chinese populations, *ERAP1* SNPs or gene variants in linkage disequilibrium with *ERAP1* SNPs were also found to be associated with psoriasis [24–26]. It is currently unclear whether the effects of *ERAP1* on psoriasis can be explained by a single variant or by allotypic associations. Recently, the association of *ERAP1* with psoriatic arthritis has also been investigated; however, this study did not demonstrate an association between rs30187 and psoriatic arthritis or psoriatic arthritis subphenotypes [27].

As psoriasis is currently best stratified by disease onset and absence or presence of arthritis, we hypothesized that stratifying psoriasis patients into early and

late onset groups, as well as skin-only and arthritis subgroups leads to the identification of new *ERAP1* genotype–phenotype associations. Furthermore, as *ERAP1* seems to be associated with inflammatory diseases in a *HLA*-dependent manner, we also intended to explore whether a gene–gene interaction between *HLA-Cw*0602* and *ERAP1* exists in these well-stratified subgroups of psoriatic patients.

Aim

Furthermore, as *ERAP1* seems to be associated with inflammatory diseases in a *HLA*-dependent manner, we also intended to explore whether a gene–gene interaction between *HLA-Cw*0602* and *ERAP1* exists in these well-stratified subgroups of psoriatic patients. We have analysed the association of five *ERAP1* and two *HLA-Cw*0602* SNPs as well as different *ERAP1* haplotypes with EOP, LOP and psoriatic arthritis.

Material and methods

Subjects

This study was approved by the Internal Review Board of the University of Szeged, the approval number is PSO-GENET-001. Informed consent was obtained from all participating patients and volunteers, and the study was conducted in full accordance with the principles of the Declaration of Helsinki. The study population consisted of 319 Hungarian Caucasian psoriasis vulgaris patients (designated as PsV) treated at the Department of Dermatology and Allergology and the Department of Rheumatology of the University of Szeged, and at the Department of Rheumatology of Pándy Kálmán Békés County Hospital, Gyula, as well as 200 ethnically-matched healthy individuals with no known multifactorial inflammatory diseases. Of the 319 psoriasis vulgaris patients, 105 exhibited psoriatic arthritis (designated as PsA), fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR). The group of patients with psoriatic arthritis was further stratified into five homogenous clinical groups according to the Moll and Wright criteria [28]. Patients with skin symptoms of psoriasis only were denoted as cutaneous psoriasis (designated as PsC) patients. Patients with onset before 40 years of age were classified as having early onset psoriasis (EO-PsV, EO-PsA, EO-PsC), whereas late onset psoriasis (LO-PsV, LO-PsA, LO-PsC) was defined by an onset at or after 40 years. The demographic and clinical characteristics of the study population are listed in Table 1.

Genotyping and haplotype analysis

Genomic DNA was isolated from venous blood of patients and controls using the BioRobot EZ and the EZ1 DNA Blood Kit from QIAGEN (Hilden, Germany), accord-

Table 1. Demographic and clinical characteristics of the study population

Characteristic	Healthy controls (N = 200)	PsV (N = 319)	PsC (N = 214)	PsA (N = 105)
Age, mean (range) [years]	40.39 ±19 (7–82)	52.13 ±21 (17–82)	50.72 ±19 (17–81)	54.34 ±13 (27–82)
Males/females [N, (%)]	77 (39)/123 (41)	177 (55)/142 (45)	125 (58)/89 (42)	52 (49)/53 (51)
PASI, mean (range)	–	–	12.42 ±16.54 (0.1–52.8)	–
Arthritis, distal [N, (%)]	–	–	–	13 (12)
Asymmetrical oligoarthritis [N, (%)]	–	–	–	28 (27)
Symmetrical polyarthritis [N, (%)]	–	–	–	45 (43)
Arthritis, axial [N, (%)]	–	–	–	19 (18)
Arthritis mutilans [N, (%)]	–	–	–	0 (0)

Table 2. ERAP1 and HLA-Cw*0602 gene SNPs

Chr.	Gene	SNP	Kit number	Nucleotide change	Variation
5	ERAP1	rs27524	C__3056837_10	A/G	None
5	ERAP1	rs27525	C__3056838_10	C/T	None
5	ERAP1	rs30187	C__3056885_10	C/T	Lys528ARG
5	ERAP1	rs17482078	C__3056871_10	C/T	Arg725Gln
5	ERAP1	rs10050860	C__3056876_10	C/T	Asp575Asn
6	HLA-C	rs10484545	C__29666895_10	C/G	None
6	HLA-C	rs10484554	C__29612773_20	C/T	None

ing to the instructions of the manufacturer. Genotyping of five SNPs of the ERAP1 gene and two SNPs of the HLA-Cw*0602 gene (Table 2), previously reported as candidate genes and SNPs in the pathogenesis of psoriasis and AS [16, 29], was carried out with the PCR-based Assay-by-Design method of Applied Biosystems (Foster City, CA), following the instructions of the manufacturer. After PCR amplification, end-point detection was performed with a CFX 96 real-time PCR machine from Bio-Rad (Hercules, CA). Genotyping of the rs10484554 SNP was used to determine the HLA-C status, as previously reported [12, 16]. Three SNPs (rs30187, rs10050860, rs17482078) were used to construct four haplotypes: Haplotype A (rs17482078/rs10050860/rs30187-CCC), Haplotype B (rs17482078/rs10050860/rs30187-CCT), Haplotype C (rs17482078/rs10050860/rs30187-TTC) and Haplotype D (rs17482078/rs10050860/rs30187-TTC, previously reported by Ombrello et al. to be risk or protective factors in AS [30].

Statistical analysis

Genotype frequencies, frequencies of the main haplotypes and SNP associations were calculated and compared between patient groups using Fisher’s exact test, using the Plink software package (v1.9). Odds ratios were calculated with 95% confidence intervals. Multiple-testing correction was applied to all comparisons using the Benjamini-Hochberg ‘FDR’ method in R (v3.2.3), with a significance threshold of $p < 0.05$. As previously suggested and successfully

applied by other authors [31–33], the age of 40 years was used for stratification of age at disease onset. No further stratification of age at disease onset was attempted due to the relatively small number of patients.

Results

The genotype frequencies of the HLA-C and ERAP1 SNPs are summarized in Table 3. Genotype frequencies in patients and controls were in Hardy-Weinberg equilibrium. Control genotype frequencies were comparable to those published in the literature. The genotype distribution of one HLA-C SNP (rs10484554) was found to be significantly different between the PsV patients and the group of healthy individuals ($p = 5.9 \times 10^{-5}$ respectively). The proportion carrying the mutant HLA-Cw*0602 allele (rs10484554 SNP) was significantly higher among PsV patients than in the group of healthy controls (58.3% and 36.5%, respectively), and there was no difference in this respect between patients with skin only or skin and joint symptoms (57.9% and 59%, respectively). Taken together, the HLA-Cw*0602 rs10484554 SNP seems to be a strong susceptibility factor for psoriasis (Table 3). In the case of the five other ERAP1 SNPs (rs27524, rs27525, rs30187, rs17482078 and rs10050860) and rs10484545 HLA-C SNP, there were no statistically detectable differences in the genotype distributions between healthy individuals and the PsV patients.

Table 3. Distribution of ERAP1 and HLA-Cw SNP genotypes in healthy controls and psoriasis patients

Healthy controls (N = 200)										PsV (N = 319)					PsC (N = 214)					PsA (N = 105)										
Gene	SNP	WT	Het	Hom rate	Disease onset	WT	Het	Hom rate	P-value*	FDR	Disease onset	WT	Het	Hom rate	P-value*	FDR	Disease onset	WT	Het	Hom rate	P-value*	FDR	Disease onset	WT	Het	Hom rate				
HLA-C	rs1048454	Total	133	143	43	5.7 × 10 ⁻⁶	5.9 × 10 ⁻⁵	90	91	33	0.00007	Total	43	52	10	0.0001	0.0007	Total	43	52	10	0.0001	0.0007	Total	43	52	10	0.0001	0.0007	
		(N = 319)	(41.7)	(44.8)	(13.5)		(N = 214)	(42.1)	(42.5)	(15.4)		(N = 105)	(41)	(49.5)	(9.5)			(N = 105)	(41)	(49.5)	(9.5)			(N = 105)	(41)	(49.5)	(9.5)			
		Early	68	96	31	7.5 × 10 ⁻⁸	1.5 × 10 ⁻⁶	46	62	24	2.1 × 10 ⁻⁶	0.0001	Early	22	34	7	0.0001	0.0001	Early	22	34	7	0.0001	0.0001	Early	22	34	7	0.0001	0.0001
		(N = 195)	(34.9)	(49.2)	(15.9)		(N = 132)	(34.8)	(47)	(18.2)	10 ⁻⁶		(N = 63)	(34.9)					(N = 63)	(34.9)					(N = 63)	(34.9)				
		Late	65	47	12	0.0707	0.2355	44	29	9	0.2570	0.6746	Late	21	18	3	0.1004	0.1757	Late	21	18	3	0.1004	0.1757	Late	21	18	3	0.1004	0.1757
		(N = 124)	(52.4)	(37.9)	(9.7)		(N = 82)	(53.7)	(35.4)				(N = 42)	(50)	(42.9)				(N = 42)	(50)	(42.9)				(N = 42)	(50)	(42.9)			
ERAP1	rs10484545	Total	272	44	3	0.4697	0.5480	183	30	1	0.9426	Total	89	14	2	0.1939	0.2026	Total	89	14	2	0.1939	0.2026	Total	89	14	2	0.1939	0.2026	
		(N = 319)	(85.2)	(13.8)			(N = 214)	(85.5)				(N = 105)	(84.7)	(13.3)				(N = 105)	(84.7)	(13.3)				(N = 105)	(84.7)	(13.3)				
		Early	165	29	1	0.9433	0.9433	109	23	0	0.5550	0.7343	Early	56	6	1	0.1400	0.1960	Early	56	6	1	0.1400	0.1960	Early	56	6	1	0.1400	0.1960
		(N = 195)	(84.6)	(14.9)			(N = 132)	(82.6)	(17.4)				(N = 63)	(88.9)					(N = 63)	(88.9)					(N = 63)	(88.9)				
		Late	107	15	2	0.1899	0.2849	74	7	1	0.0886	0.4442	Late	33	8	1	0.1332	0.1960	Late	33	8	1	0.1332	0.1960	Late	33	8	1	0.1332	0.1960
		(N = 124)	(86.3)	(12.1)			(N = 82)	(90.2)					(N = 42)	(78.6)					(N = 42)	(78.6)					(N = 42)	(78.6)				
ERAP1	rs30187	Total	125	158	36	0.2673	0.3742	82	111	21	0.5136	Total	43	47	15	0.1102	0.1543	Total	43	47	15	0.1102	0.1543	Total	43	47	15	0.1102	0.1543	
		(N = 319)	(39.2)	(49.5)	(11.3)		(N = 214)	(38.3)	(51.9)				(N = 105)	(40.9)	(44.8)	(14.3)			(N = 105)	(40.9)	(44.8)	(14.3)			(N = 105)	(40.9)	(44.8)	(14.3)		
		Early	81	94	20	0.5024	0.5553	52	67	13	0.6294	0.7343	Early	29	27	7	0.3979	0.4642	Early	29	27	7	0.3979	0.4642	Early	29	27	7	0.3979	0.4642
		(N = 195)	(41.5)	(48.2)	(10.3)		(N = 132)	(39.4)	(50.8)				(N = 63)	(46)	(42.9)				(N = 63)	(46)	(42.9)				(N = 63)	(46)	(42.9)			
		Late	44	64	16	0.1565	0.2739	30	44	8	0.5864	0.7343	Late	14	20	8	0.0436	0.1017	Late	14	20	8	0.0436	0.1017	Late	14	20	8	0.0436	0.1017
		(N = 124)	(35.5)	(51.6)	(12.9)		(N = 82)	(36.6)	(53.7)				(N = 42)	(33.4)	(47.6)				(N = 42)	(33.4)	(47.6)				(N = 42)	(33.4)	(47.6)			
ERAP1	rs10050860	Total	207	97	15	0.0249	0.1743	132	72	10	0.1103	Total	75	25	5	0.0072	0.0252	Total	75	25	5	0.0072	0.0252	Total	75	25	5	0.0072	0.0252	
		(N = 319)	(64.9)	(30.4)	(4.7)		(N = 214)	(61.7)	(33.6)				(N = 105)	(71.4)	(23.8)				(N = 105)	(71.4)	(23.8)				(N = 105)	(71.4)	(23.8)			
		Early	121	63	11	0.0418	0.2195	75	49	8	0.0877	0.4442	Early	46	14	3	0.0142	0.0663	Early	46	14	3	0.0142	0.0663	Early	46	14	3	0.0142	0.0663
		(N = 195)	(62.1)	(32.3)	(5.6)		(N = 132)	(56.8)	(37.1)				(N = 63)	(73)	(22.2)				(N = 63)	(73)	(22.2)				(N = 63)	(73)	(22.2)			
		Late	86	34	4	0.0542	0.2276	57	23	2	0.1269	0.4442	Late	29	11	2	0.0980	0.1757	Late	29	11	2	0.0980	0.1757	Late	29	11	2	0.0980	0.1757
		(N = 124)	(69.4)	(27.4)			(N = 82)	(69.5)	(28)				(N = 42)	(69)	(26.2)				(N = 42)	(69)	(26.2)				(N = 42)	(69)	(26.2)			
ERAP1	rs17482078	Total	210	93	16	0.0897	0.2355	135	69	10	0.3436	Total	75	24	6	0.0195	0.0453	Total	75	24	6	0.0195	0.0453	Total	75	24	6	0.0195	0.0453	
		(N = 319)	(65.8)	(29.2)			(N = 214)	(63.1)	(32.2)				(N = 105)	(71.4)	(22.9)				(N = 105)	(71.4)	(22.9)				(N = 105)	(71.4)	(22.9)			
		Early	123	61	11	0.1777	0.2849	78	47	7	0.4391	0.7343	Early	45	14	4	0.0356	0.0997	Early	45	14	4	0.0356	0.0997	Early	45	14	4	0.0356	0.0997
		(N = 195)	(63.1)	(31.3)	(5.6)		(N = 132)	(59.1)	(35.6)				(N = 63)	(71.4)	(22.2)				(N = 63)	(71.4)	(22.2)				(N = 63)	(71.4)	(22.2)			
		Late	87	32	5	0.0850	0.2355	57	22	3	0.2302	0.6746	Late	30	10	2	0.1608	0.2047	Late	30	10	2	0.1608	0.2047	Late	30	10	2	0.1608	0.2047
		(N = 124)	(70.2)	(25.8)			(N = 82)	(69.5)	(26.8)				(N = 42)	(71.4)	(23.8)				(N = 42)	(71.4)	(23.8)				(N = 42)	(71.4)	(23.8)			

Table 3. Cont.

Gene	Healthy controls (N = 200)				PsV (N = 319)				PsC (N = 214)				PsA (N = 105)									
	SNP	WT	Het	Hom rare	Disease onset	WT	Het	Hom rare	P-value*	FDR	Disease onset	WT	Het	Hom rare	P-value*	FDR	Disease onset	WT	Het	Hom rare	P-value*	FDR
rs27524	Total (N = 319)	125 (39.2)	152 (47.6)	42 (13.2)	0.3439	0.4248	Total (N = 214)	85 (39.7)	104 (48.6)	25 (11.7)	0.6028	0.7343	Total (N = 105)	40 (38.1)	48 (45.7)	17 (16.2)	0.2026	0.2026	0.2026	0.2026	0.2026	0.2026
	Early (N = 195)	81 (41.5)	92 (47.2)	22 (11.3)	0.7979	0.8378	Early (N = 132)	55 (41.7)	62 (47)	15 (11.3)	0.8295	0.8710	Early (N = 63)	26 (41.3)	30 (47.6)	7 (11.1)	0.8953	0.8953	0.8953	0.8953	0.8953	0.8953
	Late (N = 124)	44 (35.5)	60 (48.4)	20 (16.1)	0.1215	0.2677	Late (N = 82)	30 (36.6)	42 (51.2)	10 (12.2)	0.4854	0.7343	Late (N = 42)	14 (33.3)	18 (42.9)	10 (23.8)	0.0307	0.0997	0.0307	0.0997	0.0307	0.0997
rs27525	Total (N = 319)	108 (33.9)	211 (66.1)	0 (0)	0.1289	0.2677	Total (N = 214)	66 (30.8)	148 (69.2)	0 (0)	0.4551	0.7343	Total (N = 105)	42 (40)	63 (60)	0 (0)	0.0259	0.0453	0.0259	0.0453	0.0259	0.0453
	Early (N = 195)	67 (34.4)	128 (65.6)	0 (0)	0.1402	0.2677	Early (N = 132)	39 (29.5)	93 (70.5)	0 (0)	0.6856	0.7578	Early (N = 63)	28 (44.4)	35 (55.6)	0 (0)	0.0116	0.0663	0.0116	0.0663	0.0116	0.0663
	Late (N = 124)	41 (33.1)	83 (66.9)	0 (0)	0.2864	0.3759	Late (N = 82)	27 (32.9)	55 (67.1)	0 (0)	0.3621	0.7343	Late (N = 42)	14 (33.3)	28 (66.7)	0 (0)	0.4465	0.4808	0.4465	0.4808	0.4465	0.4808

WT – both alleles are wild type, Het – patient carrying the rare allele in one copy, Hom rare – patient carrying the rare allele in two copies; listed as [N, (%)]. *Significant compared to healthy controls.

Subsequently, psoriasis vulgaris patients were subdivided into groups according to the presence or absence of arthritis (Table 3). In line with earlier publications [29, 32, 34], the genotype distribution of the HLA-C rs10484554 SNP was found to be significantly different in both the PsC and the PsA subpopulations ($p = 0.0007$ and $p = 0.0007$, respectively), compared to healthy controls. In PsA (but not in PsC) patients, the genotype distribution of three ERAP1 SNPs (rs10050860, rs27525 and rs17482078) was also significantly different ($p = 0.0252$, $p = 0.0453$ and $p = 0.0453$, respectively) (Table 3). For all three SNPs, the proportion of patients carrying the wild type allele was higher than in the group of healthy individuals, suggesting that the rare allele of these SNPs might provide protection against the development of psoriatic arthritis. As no differences were detected in the genotype distribution of the studied ERAP1 SNPs in PsC patients, it is likely that the trend in the difference observed for the rs10050860 SNP in the PsV patients is caused by the presence of the PsA patients. No difference was detected for the ERAP1 rs27524 and rs30187 SNPs and the HLA-C rs10484545 SNP between the healthy controls and the psoriasis groups, even after stratification for arthritis.

We further stratified patients according to disease onset (early and late onset). Significant differences were observed only for the HLA-C rs10484554 SNP in the early onset groups, which is in agreement with earlier publications [13, 14, 29, 34]. This result suggests that HLA-C positivity is a susceptibility factor only for early onset psoriasis. Stratification led to no significant difference for the rs10484545 HLA-C SNP. The ERAP1 SNPs (rs10050860, rs27525 and rs17482078) known to be associated with psoriatic arthritis were found to have only a tendency in the association with EO-PsA patients ($p = 0.0663$, $p = 0.0663$ and $p = 0.0997$, respectively) (Table 3). This lends further support to the notion that the differences in distribution of these SNPs detected in the total PsA group are primarily driven by the early onset subpopulation, and that these ERAP1 SNPs presumably provide protection against early onset psoriatic arthritis.

The ERAP1 rs17482078, rs10050860, rs30187 and rs2287987 SNPs were found to be in strong linkage disequilibrium, and the association between haplotypes including these SNPs and AS was recently reported [35]. A linkage disequilibrium block containing the rs17482078/rs10050860/rs30187 SNPs was also identified in our dataset (Figure 1). Thus, we examined whether the rs17482078/rs10050860/rs30187 haplotypes were associated with psoriasis susceptibility (Table 4). We found that Haplotype B (rs17482078/rs10050860/rs30187-CCT) was a risk factor only for LO-PsV ($p = 0.0409$) and for LO-PsA ($p = 0.0413$).

As it was reported earlier that some ERAP1 variants influence psoriasis susceptibility exclusively in individuals carrying the HLA-C risk allele [12–14], we analysed

Table 4. Distribution of ERAP1 haplotypes in healthy controls and psoriasis patients

Haplotype	SNPs			Healthy controls (N = 200)				PsO (N = 319)				PsC (N = 214)				PsA (N = 105)			
	rs17482078	rs10050860	rs30187	Frequency	Disease onset	Frequency	P-value*	Disease onset	Frequency	P-value*	Disease onset	Frequency	P-value*	Disease onset	Frequency	P-value*			
A	C	C	C	38 (19)	Total (N = 319)	58 (18.2)	0.8153	Total (N = 214)	35 (16.4)	0.4804	Total (N = 105)	23 (21.9)	0.5468						
					Early (N = 195)	36 (18.5)	0.8909	Early (N = 132)	18 (13.6)	0.2015	Early (N = 63)	18 (28.6)	0.1056						
					Late (N = 124)	22 (17.7)	0.7769	Late (N = 82)	17 (20.7)	0.7389	Late (N = 42)	5 (11.9)	0.2741						
B	C	C	T	80 (40)	Total (N = 319)	148 (46.4)	0.1531	Total (N = 214)	97 (45.3)	0.2736	Total (N = 105)	51 (48.6)	0.1508						
					Early (N = 195)	84 (43)	0.5349	Early (N = 132)	57 (43.2)	0.5644	Early (N = 63)	27 (42.9)	0.6873						
					Late (N = 124)	64 (51.6)	0.0409	Late (N = 82)	40 (48.8)	0.1756	Late (N = 42)	24 (57.1)	0.0413						
C	T	T	C	47 (23.5)	Total (N = 319)	64(20)	0.5220	Total (N = 214)	45 (21)	0.7184	Total (N = 105)	19 (18.1)	0.4624						
					Early (N = 195)	43(22.1)	0.8875	Early (N = 132)	32 (24.2)	1	Early (N = 63)	11 (17.6)	0.5169						
					Late (N = 124)	21 (16.9)	0.3125	Late (N = 82)	13 (15.9)	0.3149	Late (N = 42)	8 (19)	0.7642						
D	T	T	T	33 (16.5)	Total (N = 319)	44 (13.8)	0.3985	Total (N = 214)	34 (15.9)	0.8658	Total (N = 105)	10 (9.5)	0.0962						
					Early (N = 195)	28 (14.4)	0.5560	Early (N = 132)	22 (16.7)	0.9681	Early (N = 63)	6 (9.5)	0.1742						
					Late (N = 124)	16 (12.9)	0.3798	Late (N = 82)	12 (14.6)	0.6976	Late (N = 42)	4 (9.5)	0.1842						

Frequency is listed as [N, (%)]. * Significant compared to healthy controls carrying the given haplotype.

ERAP1 SNPs in HLA-C positive psoriasis and psoriatic arthritis patients. ERAP1 SNP frequencies were compared between individuals carrying at least one copy of the risk allele of rs10484554 (HLA-C positive) and individuals not carrying the HLA-C sequence (HLA-C negative) (Table 5). Evidence for association in HLA-C positive individuals was observed for two loci. The ERAP1 rs27524 SNP in HLA-C positive individuals exhibited a 1.74-fold increased risk of PsV ($p = 0.0454$) and a 2.33-fold risk of PsA ($p = 0.0185$), in agreement with the previous report [12]. Interestingly, rs27524 by itself was not associated in our dataset with either PsV or PsC and was found to have a tendency as a susceptibility factor only for LO-PsA (Table 3). The ERAP1 rs27525 SNP decreased the risk of psoriatic arthritis development in HLA-C positive patients (odds ratio (OR) 0.42, $p = 0.0339$). Thus, the presence of the ERAP1 rs27525 SNP seems to protect HLA-C positive individuals from developing psoriatic arthritis. No other interaction was found for the ERAP1 rs30187, rs10050860 and rs17482078 SNPs in HLA-C positive individuals, even after further stratifying the patients into early and late onset subgroups.

Discussion

Psoriasis has been associated with the PSORS1 disease susceptibility locus of the MHC class I region on chromosome 6. Within PSORS1, the HLA-Cw6 gene has shown the strongest association with psoriasis [8]: about 60% of psoriasis patients carry the HLA-Cw*0602

allele. HLA-C positive patients exhibit earlier disease onset, higher incidence of guttate and eruptive type of psoriasis, more extensive disease symptoms, and more frequent exacerbations caused by throat infections than HLA-C negative individuals. The frequency of HLA-Cw*0602 is significantly lower in patients with psoriatic arthritis compared with those with psoriasis alone, and its presence is associated with a longer psoriasis–arthritis interval and milder arthritis forms [34, 36, 37].

In this study, a well-characterized cohort of psoriasis patients was available for investigating whether HLA-Cw6 or ERAP1 gene polymorphisms are associated with different clinical phenotypes of psoriasis and psoriatic arthritis. Our dataset included patients with early and late onset psoriasis vulgaris, as well as with cutaneous psoriasis and psoriatic arthritis.

Our results confirmed the previously reported genetic association of psoriasis with both HLA-Cw6 and ERAP1 genes [12–14]. The HLA-Cw*0602 rs10484554 SNP was found to have a very strong association with PsV, and the association was highly significant with both PsC and PsA groups as well (although somewhat stronger with PsC). Interestingly, only EO-PsV was associated with HLA-C in our dataset. Previously, the HLA-Cw*06 allele was not found to be a risk factor for late onset psoriasis in a Northern Polish population [38], and late onset psoriasis demonstrated only a weak association with HLA-Cw*06 alleles in other studies [13, 39]. More recently, however, a study using dense genotyping revealed that HLA-Cw*06 is associated with late onset psoriasis [40].

Table 5. HLA-C and ERAP1 interactions in psoriasis and psoriatic arthritis

ERAP1 SNP	PsV (N = 319)				PsC (N = 214)				PsA (N = 105)			
	Disease onset	P-value*	OR	95% CI	Disease onset	P-value*	OR	95% CI	Disease onset	P-value*	OR	95% CI
rs30187	Total (N = 319)	0.0506	1.72	0.99–2.97	Total (N = 214)	0.0869	1.66	0.93–2.98	Total (N = 105)	0.0818	1.84	0.92–3.67
	Early (N = 195)	0.0643	1.73	0.97–3.09	Early (N = 132)	0.0837	1.74	0.93–3.28	Early (N = 63)	0.1812	1.70	0.78–3.69
	Late (N = 124)	0.1342	1.70	0.85–3.41	Late (N = 82)	0.3197	1.49	0.68–3.29	Late (N = 42)	0.1302	2.17	0.79–6.00
rs10050860	Total (N = 319)	0.2402	0.72	0.41–1.25	Total (N = 214)	0.3092	0.73	0.40–1.33	Total (N = 105)	0.2893	0.68	0.34–1.39
	Early (N = 195)	0.2550	0.71	0.39–1.28	Early (N = 132)	0.4206	0.77	0.40–1.46	Early (N = 63)	0.2090	0.59	0.26–1.34
	Late (N = 124)	0.3967	0.74	0.36–1.50	Late (N = 82)	0.3266	0.66	0.29–1.51	Late (N = 42)	0.8050	0.88	0.33–2.39
rs17482078	Total (N = 319)	0.2080	0.70	0.40–1.22	Total (N = 214)	0.2568	0.71	0.39–1.29	Total (N = 105)	0.2893	0.68	0.34–1.39
	Early (N = 195)	0.2550	0.71	0.39–1.28	Early (N = 132)	0.3374	0.73	0.38–1.39	Early (N = 63)	0.3209	0.67	0.30–1.49
	Late (N = 124)	0.2931	0.68	0.33–1.40	Late (N = 82)	0.3266	0.66	0.29–1.51	Late (N = 42)	0.5211	0.72	0.26–1.99
rs27524	Total (N = 319)	0.0454	1.74	1.01–3.01	Total (N = 214)	0.1572	1.52	0.85–2.72	Total (N = 105)	0.0185	2.33	1.15–4.72
	Early (N = 195)	0.0592	1.75	0.98–3.13	Early (N = 132)	0.1587	1.57	0.84–2.95	Early (N = 63)	0.0500	2.21	0.99–4.94
	Late (N = 124)	0.1238	1.73	0.86–3.48	Late (N = 82)	0.3905	1.41	0.64–3.12	Late (N = 42)	0.0730	2.57	0.90–7.36
rs27525	Total (N = 319)	0.1502	0.64	0.35–1.18	Total (N = 214)	0.3682	0.74	0.38–1.43	Total (N = 105)	0.0516	0.48	0.23–1.01
	Early (N = 195)	0.1142	0.60	0.31–1.14	Early (N = 132)	0.3473	0.72	0.36–1.44	Early (N = 63)	0.0339	0.42	0.19–0.94
	Late (N = 124)	0.4530	0.75	0.35–1.61	Late (N = 82)	0.6254	0.80	0.33–1.94	Late (N = 42)	0.4278	0.65	0.23–1.87

*Individuals carrying at least one copy of the rare allele of the rs10484554 HLA-C SNP and both wild type alleles of the indicated ERAP1 SNP (HLA-C positive/ERAP1 negative) are compared with individuals carrying at least one copy of the rare allele of the rs10484554 HLA-C SNP and at least one copy of the rare allele of the indicated ERAP1 SNP (HLA-C positive/ERAP1 positive).

Genetic variants of ERAP1 have recently been reported to be associated with psoriasis [13, 14, 16]. ERAP1 trims peptides imported into the endoplasmic reticulum at their N-terminus and contributes to the shaping of the antigenic repertoire presented by class I MHC molecules [19]. The association of ERAP1 with psoriatic arthritis has previously been investigated; however, no association between ERAP1 SNPs and psoriatic arthritis or psoriatic arthritis subphenotypes was identified [27]. Recently, ERAP1 association with psoriasis was detected in patients with an age of onset between 10 and 20 years, and no association was detected in cases with onset below 10 years [16].

Our results suggest that the HLA-C rs10484554 SNP contributes to psoriasis susceptibility. The proportions of the rare alleles of the ERAP1 rs27525, rs17482078 and rs10050860 SNPs were higher in the group of healthy individuals, suggesting that individuals with the rare alleles of these SNPs might be protected against psoriasis. These associations were also apparent when groups of psoriatic patients were analysed separately according to the presence or absence of arthritis. The stratification of the patients for early (< 40 years) or late (≥ 40 years) disease onset revealed an age-dependent difference in the genetic background of psoriasis: the associations with these SNPs tend to be stronger in patients with early disease onset.

Although ERAP1 was neither dependent on nor interacting with HLA-C*06:02 in certain populations, an interaction between HLA-C and ERAP1 was reported recently

and confirmed several times subsequently [9, 12–14]. Interestingly, dominant epistasis between HLA-Cw*0602 and one of the ERAP1 SNPs was identified recently in psoriasis [23].

Recent studies of the ERAP1 rs27524 SNP reported association with the pathogenesis of psoriasis, especially in the group with age of disease onset between 10 and 20 years [16, 41]. Our results revealed only a trend in association with the late disease onset group, for which it might increase the likelihood of psoriasis development. No association with psoriasis was observed for the ERAP1 rs30187 SNP in this study, which is in contrast with previous studies [12, 16]; however, Jadon *et al.* also reported that there was no association with psoriatic arthritis [27]. In addition, this psoriasis-risk allele, which is common in the European population, was not associated with the disease in an East Asian population [24].

Psoriatic arthritis patients, especially in the early onset group, carrying the ERAP1 rs27525 and rs17482078 SNPs seem to be protected from the subsequent development of the disease. Individuals carrying the rare allele of the ERAP1 rs10050860 SNPs might be protected against psoriasis, but this effect was more prominent among patients with psoriatic arthritis, especially in the early onset group. These findings suggest that these three SNPs (rs27525, rs17482078, rs10050860) might be protective against psoriatic arthritis.

The two coding ERAP1 SNPs (rs17482078 and rs10050860) and the rs30187 SNP are in linkage disequilibrium (Figure 1) and have been reported as a pro-

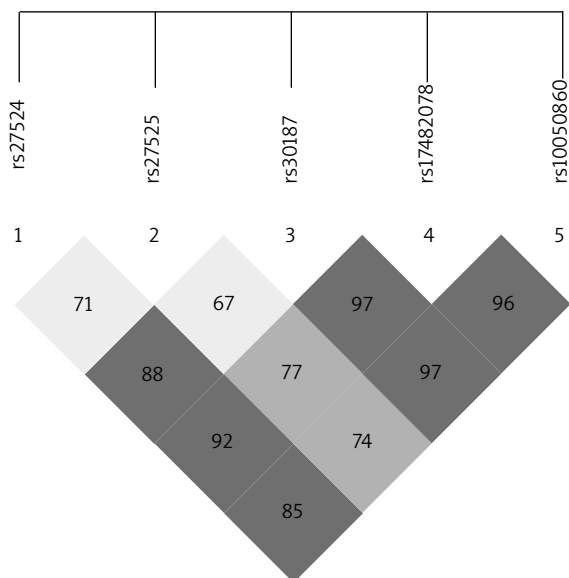


Figure 1. Linkage disequilibrium (LD) for the ERAP1 SNPs in the study population

tective haplotype (rs17482078/rs10050860/rs30187/rs2287987–TTCC) in *HLA-B* positive AS patients [35]. Also the rs17482078/rs10050860/rs30187–CCT haplotype was confirmed as a risk factor for AS [42] in an AS population in Belgium, which we examined as Haplotype B (rs17482078/rs10050860/rs30187–CCT) in psoriasis susceptibility similarly to AS [35], and it was found to be a risk factor for only LO-PsV ($p = 0.0409$) and LO-PsA ($p = 0.0413$). We were unable to find any association with psoriasis or with psoriatic arthritis for Haplotype A (rs17482078/rs10050860/rs30187–CCC), Haplotype C (rs17482078/rs10050860/rs30187–TTC) and Haplotype D (rs17482078/rs10050860/rs30187–TTC). These data suggest that the Haplotype B conferring disease risk in AS also influences susceptibility to joint involvement in psoriasis.

Genome-wide association studies identified the interaction between the *ERAP1* rs27524 SNP and the *HLA-C* rs10484554 SNP; this interaction was the most prominent among individuals carrying one or two copies of the risk allele at rs10484554 [12]. In subsequent analysis, the association with *ERAP1* was not restricted to individuals carrying *HLA-Cw*0602*; however the genetic association with *ERAP1* (rs207524, rs30187, rs26653) in psoriasis was confined to individuals with an age of disease onset between 10 and 20 years [16]. In a Polish population, *ERAP1* rs27524 SNP was a susceptibility factor for *HLA-C* positive patients with late onset psoriasis [13]. In our study, the *ERAP1* rs27524 SNP in *HLA-C* positive individuals caused a 1.74-fold increased risk of PsV ($p = 0.0454$) and a 2.33-fold risk of PsA ($p = 0.0185$). Notably, the rs27524 SNP by itself was not associated either with PsV or with PsC in this dataset and was found to have only a tendency

as a susceptibility factor for LO-PsA (Table 3). The *ERAP1* rs27525 SNP in *HLA-C* positive patients decreased the risk of psoriatic arthritis development (OR = 0.42, $p = 0.0339$); thus, the presence of these SNPs seems to protect against developing psoriatic arthritis.

Taken together, our results suggest that the genetic variants of the *ERAP1* and *HLA-C* genes contribute to the pathogenesis of psoriasis in a manner that is dependent on age of onset. Individuals with *HLA-Cw*0602* are more prone to early onset of disease (before 40 years), confirming that onset after 40 years represents a biologically valid approximation for a genetically distinct subgroup of psoriasis. The overall psoriasis group was stratified by various clinical aspects, including the age of onset and the presence or absence of psoriatic arthritis. This novel and careful stratification of patients according to the symptoms and age of onset leads to important insights for psoriasis, a heterogeneous, multifactorial disease, and might become more important for further research as well as for personalized medicine.

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Conflict of interest

The authors declare no conflict of interest.

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