HLA-B*27 is significantly enriched in Nordic patients with psoriatic arthritis mutilans

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Abstract

Objective

The genetic contribution to psoriatic disease is substantial with a dominating influence of the HLA region. The profile of HLA class I genotypes likely contributes to shaping clinical phenotypes. Herein we aimed to explore such genotypes in cohorts of closely characterised subsets of psoriatic disease with special focus on psoriatic arthritis mutilans (PAM), a severe and rare form of psoriatic arthritis (PsA).

Methods

Cohorts of patients with the diagnosis of psoriasis vulgaris with or without arthritis (n=1217), psoriasis without arthritis (n=534), psoriatic arthritis without mutilating disease (n=337) and psoriatic arthritis mutilans (n=63) were collected and genotyped for HLA class I and II genes, with standardised methodologies. Cases were compared with a healthy control population (n=2468). Case-only and case-control association tests were performed to address the hypothesis of genetic contribution to clinical phenotypes.

Results

*The presence of HLA-B*27 was strikingly increased in PAM (45%) compared with PsA without mutilating disease (13%) and with healthy controls (13%). However, within the PAM population, HLA-B*27 did not correlate with clinical markers such as number of mutilating joints, radiographic scoring, disease duration and age of disease onset.*

Conclusion

*HLA-B*27 emerges as an important genotype marker for PAM.*

Key words

psoriasis, arthritis, mutilans, HLA-B*27, HLA-genotyping

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Introduction

Psoriatic arthritis mutilans (PAM) is a rare and severe subgroup of psoriatic arthritis (PsA) (Fig. 1) (1). PAM primarily affects small joints in fingers and toes and is characterised by destructive bone loss, osteolysis, causing permanent damage and resulting in short functionally impaired digits (2-5). Although the general form of PsA that belongs to the spondyloarthropathies (SpA) (6) affects less than 0.5% of the general population, PAM represents the most extreme and distressing type of PsA (7-8). Despite the fact that the ethiology of PAM is unknown, there is little doubt about its autoimmune origin. The genetic contribution of the HLA locus to autoimmune disorders is well established (9). Previous conference communication by Chandran *et al*. suggested that HLA-B*27 and -DQB1*02 are associated with increased risk of developing mutilating disease in PsA in Canadian Caucasians (10) but neither this study has appeared as a full article, nor have further studies validating this finding been published. Genetic studies suggest that specific HLA genotypes likely contribute to shaping the clinical outcome in psoriatic disease (11) and careful clinical stratification of disease phenotypes may be highly informative. Herein, we compare, HLA genotypes including HLA-A, -B, -C, -DRB1 and -DQB1 genes in Swedish cohorts of patients with psoriatic disease; cutaneous psoriasis without arthritis (PsC), psoriasis vulgaris with and without arthritis (PsV), psoriasis arthritis without mutilating disease (PsA) and in a Nordic cohort of psoriatic arthritis mutilans (PAM).

Methods

Samples

We recruited 63 case subjects with PAM for this study from the Nordic PAM Study (5-12) (Table I). The PAM patients underwent thorough clinical examination by specialists in rheumatology and dermatology and the diagnosis of PAM was verified by radiography (13). The cohorts have been described (12) with the clinical phenotype in agreement with the GRAPPA (**G**roup for **R**esearch and **A**ssessment of **P**soriasis and **P**soriatic **A**rthritis) consensus statement on arthritis mutilans (14). No patient was diagnosed with AS (5-12). From Sweden we included 1217 PsV cases who were all diagnosed with chronic plaque psoriasis by dermatologists at the department of Dermatology at Karolinska University Hospital, Sweden. Of these, 337 patients were also diagnosed with concomitant PsA by rheumatologists while 534 had cutaneous psoriasis without arthritis, PsC (Table I). The study was approved by ethical review boards at each institution and conducted according to the Declaration of Helsinki Principles. Patients and controls gave their informed consent and for children younger than 18 years of age, consent was also obtained from their parents. Healthy controls were recruited from the Epidemiological Investigation of Rheumatoid Arthritis study (EIRA study; n=1001) (15). Additionally, we used DNA from 450 Swedish matched controls as well as 1017 blood donors for genotyping of rs4349859.

Radiographic scoring

The radiographs were scored by one reader (LL) blinded for the clinical findings using two documented and validated methods: the modified Sharp-van der Heijde method (mSvdH) and the Psoriatic Arthritis Ratingen Score (PARS) (13-16). In addition to joints included in the scoring systems, all small joints in the hands and feet were evaluated for the occurrence of radiologically mutilated joints (13).

Genotyping

Peripheral blood samples were collected, and genomic DNA extracted by standard procedures. We used the following genotyping methods: 1) HLA-C*06 was analysed as described by Nikamo *et al*. 2012 (17), 2) PCR-SSP Olerup SSP® with HLA-combi-kit A-B-C and HLA-combi-kit DR-DQ according to the manufacturer's instructions (CareDx international AB, Sweden) (18) and analysis was performed in SCORE™ software and 3) GWAS data was HLA imputed according to Leslie *et al*. (19). 4) The SNP rs4349859 was genotyped on the QuantStudio 7 Flex

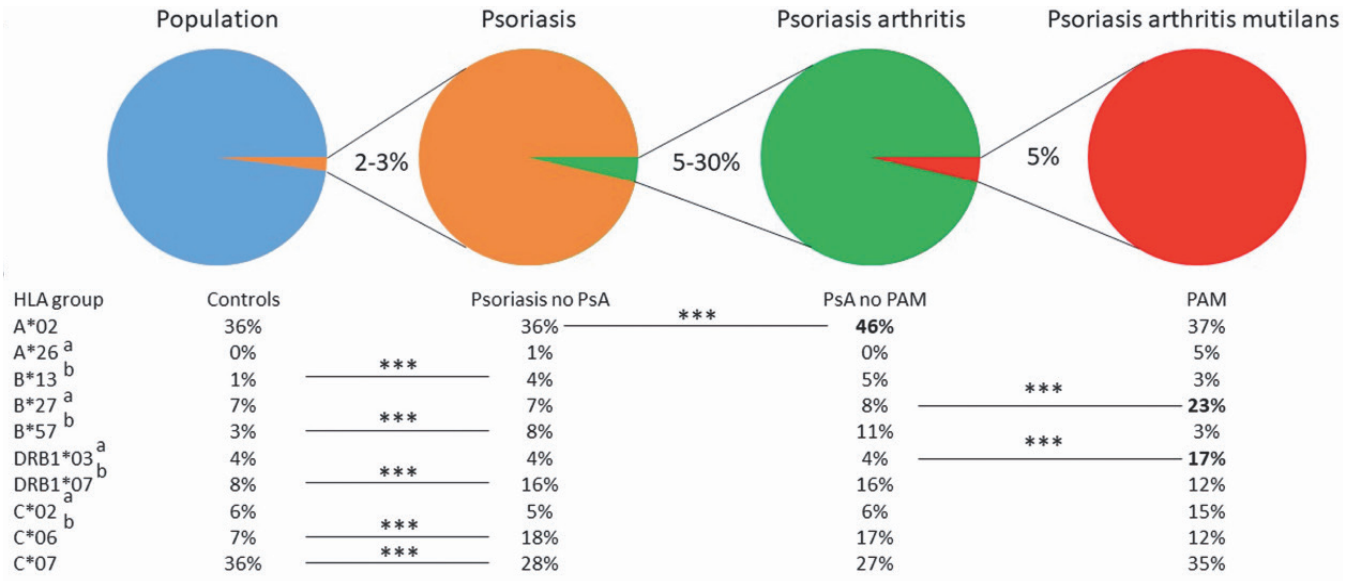

Fig. 1. A: Population distribution of psoriasis, psoriatic arthritis and psoriasis arthritis mutilans.
Controls (blue), Psoriasis without arthritis (orange), Psoriatic arthritis (green), and Psoriasis arthritis mutilans (red).
B: Allele frquencies and associations of selected HLA groups in our cohort.
Statistical sigificance of <0.001(***) when comparing [a]Psoriasis arthritis mutilans with Psoriasis and Controls as well as [b]Psoriatic arthritis with Controls.

Table I. Population characteristics of the sample set.

Clinical characteristics	Subjects	Female [n (%)]	Mean age at onset (range)	HLA-Cw*06 positive [n (%)][&]	HLA-B*27 positive [n (%)][#]	rs4349859 positive [n (%)][¤]	HLA-Cw*06 allele frequency [n (%)][&]	HLA-B*27 allele frequency [n (%)][#]	rs4349859 allele frequency [n (%)][¤]
PsV Discovery	557	313 (56)	34 (1-84)	199 (36)	71 (14)	74 (13)	210 (19)	73 (7)	76 (7)
PsV Confirmation	660	262 (40)	32 (1-79)	242 (37)	NA	85 (13)	254 (19)	NA	88 (7)
PsV All	1217	575 (47)	33 (1-84)	441 (36)	74 (13)	159 (13)	464 (19)	76 (7)	164 (7)
PsC Discovery	292	159 (54)	30 (1-80)	103 (38)	35 (13)	36 (12)	120 (21)	35 (7)	36 (6)
PsC Confirmation	243	93 (38)	34 (1-74)	99 (41)	NA	35 (7)	103 (21)	NA	33 (14)
PsC All	534	252 (47)	32 (1-80)	212 (40)	35 (13)	69 (13)	223 (21)	35 (7)	71 (7)
PsA Discovery	102	55 (54)	34 (1-70)	34 (33)	13 (13)	14 (14)	34 (17)	15 (8)	16 (8)
PsA Confirmation	235	93 (40)	29 (4-60)	80 (34)	NA	29 (12)	87 (19)	NA	29 (6)
PsA All	337	148 (44)	30 (1-80)	114 (34)	13 (13)	43 (13)	122 (18)	15 (8)	45 (7)
PAM	63	32 (51)	39 (6-65)	13 (22)	27 (45)	28 (44)	14 (12)	27 (23)	28 (22)
EIRA Controls	1001	723 (72)	52 (18-70)	128 (13)	133 (13)	54 (14)¤	131 (7)	134 (7)	57 (7)¤
Swedish controls[1]	450	262 (58)	46 (15-88)	46 (10)	NA	63 (14)	50 (6)	NA	64 (7)
Swedish controls[2]	1017	504 (50)	(18-65)	147 (14)	NA	111 (11)	152 (7)	NA	116 (6)

[#]Imputed data and Olerup typed data; [&]Typing according to Nikamo and Ståhle (2012); [1]Swedish matched controls; [2]Swedish blood donors; NA: not available; [¤]Only 398 EIRA controls have genotypes for rs4349859.

Real-Time PCR System Instrument by using allele specific Taqman MGB probes labelled with fluorescent dyes FAM and VIC (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's protocols. Allelic discrimination was made with the QuantStudio™ Real-Time PCR Software (Applied Biosystems).

Statistics

Case-control analyses were performed to test association comparing subtypes of psoriasis with population controls. Case-only analyses were used to compare subtypes with each other. Both case-control and case-only analyses were tested for allele frequency differences for all SNPs using logistic regression with gender as covariate. Associations between genetic markers and disease status were analysed using the PLINK v. 1.07 (20). Haplotypes were analysed using Unpahsed 3.1.7 (21). We have highlighted *p*-values that would remain significant after correction for multiple testing using the adjust mode as implemented in PLINK v. 1.07 (20). For the case-only association we have adjusted for stratification into four cohorts; PsV, PsC, PsA and PAM, using the Sidák correction (22), where *p*-values are adjusted using simple functions of the number of tested hypotheses. For haplotype analysis, Sidák correction was also used to adjust for multiple testing. Stratification for HLA-B*27 positive and negative PAM patients and comparing clinical data was performed with One-way ANOVA with significance level 0.05.

Results

First, we performed case-control association tests for the PAM subgroup in

Table II. Case-control study.

HLA	PsV *vs*. controls		PsC *vs*. controls		PsA *vs*. controls		PAM *vs*. controls	
	p-value	OR (CI)	*p*-value	OR (CI)	*p*-value	OR (CI)	*p*-value	OR (CI)
A*01	0.92	1.01 (0.82-1.24)	0.15	1.20 (0.93-1.55)	0.34	0.80 (0.51-1.26)	0.04	1.66 (1.04-2.67)
A*02	0.82	0.98 (0.84-1.15)	0.02	0.78 (0.63-0.95)	0.008	1.48 (1.11-1.98)	0.85	1.04 (0.71-1.52)
A*23	0.69	0.82 (0.40-1.69)	0.81	0.90 (0.37-2.20)	0.76	0.79 (0.18-3.44)	0.02	3.52 (1.27-9.77)
B*08[¤]	0.005	0.70 (0.54-0.90)	0.02	0.67 (0.48-0.93)	0.07	0.62 (0.37-1.05)	0.29	1.32 (0.79-2.19)
B*13	**2×10^{-7}**	4.33 (2.49-7.51)	**4×10^{-6}**	4.41 (2.34-8.29)	**0.0001**	5.05 (2.21-11.55)	0.17	2.41 (0.68-8.48)
B*27	0.59	1.09 (0.81-1.47)	0.90	1.03 (0.69-1.52)	0.59	1.17 (0.67-2.03)	**2×10^{-9}**	4.74 (2.85-7.89)
B*37	0.003	2.27 (1.32-3.92)	0.005	2.49 (1.32-4.70)	0.78	0.81 (0.19-3.49)	0.01	3.67 (1.13-10.10)
B*57	**3×10^{-9}**	2.87 (2.03-4.07)	**2×10^{-7}**	2.99 (1.98-4.52)	**1×10^{-8}**	3.96 (2.28-6.87)	0.94	1.04 (0.36-2.99)
DRB1*01	0.96	0.99 (0.79-1.25)	0.98	1.00 (0.75-1.34)	0.50	0.84 (0.52-1.36)	0.08	1.59 (0.94-2.66)
DRB1*03	0.76	1.06 (0.72-1.57)	0.04	1.58 (1.02-2.45)	0.91	1.04 (0.49-2.24)	**7×10^{-8}**	5.36 (2.91-9.87)
DRB1*07	**7×10^{-10}**	2.09 (1.65-2.64)	**3×10^{-7}**	2.12 (1.59-2.82)	**0.0002**	2.19 (1.44-3.33)	0.18	1.52 (0.83-2.80)
DRB1*08	0.84	1.04 (0.71-1.52)	0.25	0.73 (0.42-1.26)	0.02	1.99 (1.12-3.56)	0.29	1.57 (0.68-3.60)
DRB1*09	<0.05	1.76 (1.01-3.08)	0.02	2.14 (1.12-4.12)	0.32	0.36 (0.05-2.69)	0.67	1.38 (0.32-6.00)
DRB1*10	0.05	5.10 (0.97-26.74)	0.66	5.52 (0.89-34.20)	0.12	6.80 (0.60-76.23)	0.03	13.87 (1.22-157.80)
DQB1*02	0.27	1.11 (0.92-1.33)	0.06	1.24 (0.99-1.56)	0.59	1.10 (0.77-1.58)	0.12	1.43 (0.91-2.25)
DQB1*04	0.48	0.87 (0.59-1.28)	0.06	0.57 (0.32-1.02)	0.03	1.88 (1.06-3.34)	0.34	1.15 (0.65-3.44)
C*01	0.91	0.98 (0.68-1.42)	0.52	0.85 (0.52-1.39)	0.22	0.56 (0.23-1.40)	0.05	1.98 (1.00-3.92)
C*02	0.42	0.87 (0.63-1.22)	0.61	0.90 (0.59-1.37)	0.95	0.98 (0.52-1.82)	**0.0002**	2.93 (1.66-5.16)
C*06	**9×10^{-22}**	3.41 (2.65-4.38)	**2×10^{-18}**	3.80 (2.82-5.12)	**6×10^{-7}**	3.04 (1.96-4.70)	0.05	1.83 (1.01-3.33)
C*07[£]	**1×10^{-5}**	0.70 (0.59-0.82)	**2×10^{-5}**	0.63 (0.51-0.78)	0.01	0.66 (0.48-0.92)	0.77	0.94 (0.64-1.39)

CI: confidence interval; OR: odds ratio.
p-values in bold are significant after correction for multiple testing using the adjust mode as implemented in PLINK v. 1.07 (20) ($p<0.05$).
[£]C*07 protects for PsV, PsC and PsA compared to controls; [¤]B*08 protects for PsV and PsC compared to controls.

Table III. Case-case study.

HLA	PAM *vs*. PsV		PAM *vs*. PsC		PAM *vs*. PsA		PsA *vs*. PsC	
	p-value	OR (CI)	*p*-value	OR (CI)	*p*-value	OR (CI)	*p*-value	OR (CI)
A*01	0.09	1.46 (0.94-2.28)	0.32	1.26 (0.80-2.00)	0.02	2.14 (1.11-4.14)	0.12	0.70 (0.45-1.10)
A*02	0.79	1.05 (0.73-1.53)	0.22	1.29 (0.86-1.92)	0.16	0.73 (0.47-1.13)	**0.0002**	1.86 (1.34-2.60)
A*23	0.02	3.44 (1.22-9.72)	<0.05	3.18 (1.00-10.11)	0.09	4.42 (0.81-24.06)	0.91	0.92 (0.22-3.93)
A*26	**0.0002**	8.84 (2.85-27.48)	**0.01**	4.38 (1.41-13.65)		NA		NA
B*08	0.02	1.87 (1.10-3.18)	0.02	2.00 (1.11-3.60)	0.04	2.17 (1.05-4.47)	0.77	0.91 (0.51-1.65)
B*13	0.45	0.63 (0.18-2.10)	0.40	0.59 (0.17-2.03)	0.35	0.53 (0.14-2.03)	0.79	1.12 (0.49-2.52)
B*27	**3×10^{-8}**	4.78 (2.74-8.32)	**5×10^{-8}**	5.88 (3.11-11.11)	**0.0002**	4.09 (1.96-8.52)	0.63	1.17 (0.62-2.18)
B*37	0.44	1.45 (0.56-3.76)	0.60	1.31 (0.49-3.50)	0.08	4.49 (0.84-23.98)	0.14	0.33 (0.08-1.42)
B*57[#]	0.07	0.38 (0.14-1.08)	0.07	0.37 (0.13-1.07)	0.02	0.27 (0.09-0.83)	0.34	1.32 (0.75-2.33)
DRB1*01	0.10	1.55 (0.93-2.60)	0.12	1.53 (0.89-2.63)	<0.05	2.08 (1.01-4.31)	0.51	0.84 (0.50-1.41)
DRB1*03	**7×10^{-7}**	4.85 (2.60-9.05)	**0.0002**	3.41 (1.78-6.54)	**0.0006**	5.05 (2.01-12.65)	0.38	0.70 (0.31-1.55)
DRB1*07	0.39	0.77 (0.42-1.40)	0.32	0.73 (0.39-1.36)	0.37	0.72 (0.35-1.48)	0.94	1.02 (0.66-1.58)
DRB1*08	0.31	1.53 (0.67-3.51)	0.09	2.27 (0.89-5.80)	0.55	0.75 (0.30-1.91)	**0.006**	2.74 (1.35-5.59)
DRB1*09	0.74	0.78 (0.18-3.39)	0.60	0.67 (0.15-3.03)	0.30	3.60 (0.32-40.87)	0.09	0.18 (0.02-1.35)
DRB1*10	0.52	2.04 (0.23-17.84)	0.66	1.68 (0.17-16.44)	0.62	2.04 (0.12-33.90)	0.94	0.92 (0.09-8.97)
DQB1*02	0.29	1.26 (0.82-1.94)	0.56	1.14 (0.73-1.79)	0.40	1.28 (0.73-2.25)	0.62	0.91 (0.63-1.32)
DQB1*04	0.21	1.70 (0.74-3.91)	0.04	2.75 (1.05-7.19)	0.56	0.76 (0.30-1.92)	**0.002**	3.25 (1.54-6.87)
C*01	0.03	2.24 (1.06-4.74)	0.02	2.63 (1.16-5.98)	0.02	3.89 (1.26-12.01)	0.42	0.66 (0.24-1.82)
C*02	**6×10^{-5}**	3.36 (1.85-6.09)	**0.0003**	3.38 (1.75-6.55)	**0.01**	2.81 (1.29-6.13)	0.79	1.10 (0.55-2.20)
C*06	0.08	0.59 (0.32-1.07)	0.03	0.51 (0.28-0.95)	0.21	0.64 (0.32-1.28)	0.33	0.80 (0.51-1.25)
C*07	0.12	1.37 (0.92-2.05)	0.06	1.51 (0.98-2.31)	0.15	1.46 (0.88-2.42)	0.78	1.05 (0.73-1.52)

p-values in bold are significant after correction for multiple testing using the Sidák correction (22) ($p<0.05$).
[#]HLA-B*57 risk in PsA compared to PAM; NA: not analysed due to lack of HLA-A*26 alleles in the PsA patients.

our study. The analysis of PAM compared with controls revealed significant associations to HLA-B*27, -DRB1*03 and -C*02 (Table II, Fig. 1), with the latter association to PAM reported for the first time. Second, we performed case-only association tests for PAM and other disease subgroups in our study. Similar to case-control association the same risk alleles (HLA-B*27, -DRB1*03 and -C*02) were associated when analysing PAM to PsV, PsC and PsA (Table III). Herein we show that 45% of the PAM patients were HLA-B*27 positive, compared with 13% in the PsA cohort. There was no difference between HLA-B*27 positive and negative patients regarding clinical parameters such as number of mutilated joints evaluated by radiography (13), gender, age at onset, disease duration,

family history of PsA measured as affected first degree relatives, psoriasis skin severity measured by Psoriasis Area Severity Index (PASI) or smoking (Table IV). The majority of patients were on systemic therapy (5) with no difference between HLA-B*27 positive and negative patients.

When analysing specifically HLA-B*27 negative individuals, HLA-DRB1*03 associates to PAM compared to controls (p=2x10^{-7} OR 7.46 [CI 3.50–15.91]) as well as compared to PsA (p=0.0007 OR 6.10 [CI 2.15–17.31]).

HLA-A*26 shows association to PAM when comparing to PsV and PsC. However, the population frequency of HLA-A*26 is very low with only a small number of patients carrying HLA-A*26; six individuals with PAM (5%), seven with PsC (3%), none with PsA and only one of the controls. Thus, firm conclusions would require a significantly larger sample size. Of potential interest is the finding that, five of six PAM patients positive for HLA-A*26 all carry HLA-A*01 as a second allele with a closer look revealing an extended haplotype of HLA-A*01-B*08-DRB1*3-DQB1*2-C*07 when comparing PAM with PsV (Table V). HLA-B*57 shows association in PsA compared to PAM (Table III).

When analysing PsV, PsC and PsA cohorts compared with controls we confirm previously reported associations to HLA-B*13, -B*57, -DRB1*07 and -C*06 (Table II). However, when comparing PsA to PsC we find additional associated alleles; HLA-A*02, -DRB1*08 and -DQB1*04 (Table III).

Table IV. Stratification by HLA-B*27 positive and negative PAM patients.

	HLA-B*27 positive Mean	HLA-B*27 negative Mean	p-value	SD
Age at onset PSO	28	24	0.35	15.25
Age at onset PsA	32.7	29	0.32	12.87
Disease duration PSO-PsA	4.7	5.5	0.82	11.96
Disease duration PSO-today	46.8	45.8	0.81	16.42
Disease duration PsA-today	43.5	41.1	0.58	16.43
PASI	4.28	5.04	0.08	6.19
Number of mutilated joints[#]	16.5	15.3	0.69	10.23
PARS total score	116.1	137.1	0.37	80.54
mSvdH total score	198.6	230.0	0.43	138.73
	n (%)	n (%)	p-value	Chi-square
Sex: Female	17 (61)	15 (43)	0.16	1.98
Family history PsA	8 (30)	10 (33)	0.76	0.09
Smoking	6 (27)	14 (47)	0.16	2.02

PARS: Psoriatic Arthritis Ratingen Score; mSvdH: Sharp-van der Heijde modified scoring method.
[#]Number of mutilated joints evaluated by radiographic scoring.

Table V. Haplotype association between subgroups.

Haplotype	Cases n (%)	Controls n (%)	p-value (p for risk haplotype)	OR (CI)
PAM *vs*. PsA				
B*27-C*01	9 (7.4)	3 (1.5)	**0.002 (0.007)**	5.93 (1.50-23.39)
A*01-B*08-DRB1*03-DQB1*02-C*07	8 (8)	3 (1.5)	**0.001 (0.003)**	5.98 (1.45-24.79)
B*08-DRB1*03-DQB1*02-C*07	14 (14)	4 (2)	**0.0003 (0.0002)**	6.68 (2.09-21.34)
PAM *vs*. PsV				
A*01-DRB1*03	10 (10)	18 (2)	**4 x 10^{-5} (5 x 10^{-12})**	6.61 (2.79-15.64)
B*08-DRB1*03-C*07	14 (14)	22 (2)	**6 x 10^{-6} (9 x 10^{-11})**	6.95 (3.36-14.35)
B*08-DRB1*03-DQB1*02-C*07	14 (14)	20 (2)	**2 x 10^{-6} (4 x 10^{-11})**	7.18 (3.38-15.24)
PAM *vs*. Controls				
A*01-DRB1*03	10 (10)	35 (2)	**2 x 10^{-5} (3 x 10^{-17})**	6.54 (2.96-14.49)
B*08-DRB1*03	14 (14)	46 (2)	**7 x 10^{-7} (7 x 10^{-14})**	6.47 (3.39-12.37)
DRB1*03-C*07	13 (13)	48 (2)	**2 x 10^{-6} (3 x 10^{-17})**	5.39 (2.70-10.77)

Discussion

Our study shows association of HLA-B*27, -DRB1*03 and -C*02 alleles with PAM in the Nordic population. Clinical phenotyping and diagnosis of diseases is often difficult and relies predominantly on parameters that are obvious to the eye but lack deep molecular and genetic fingerprinting. To improve and better understand how phenotypes should be grouped in terms of disease expression, severity and response to therapy, genetic profiling has emerged as an important tool. For common diseases such as psoriasis, large-scale genome wide studies have successfully identified a string of genetic variants, which are in line with putative drug targets and the successful development of effective therapies. Genotyping of such large clinical cohorts serves to identify main common pathways but may not reveal less common but important differences defining specific profiles within the larger groups. Considering the importance of the HLA cluster in psoriasis and PsA, we undertook the present study to investigate HLA profiles of stratified patient cohorts with respect to PAM.

Patients were collected within Swedish dermatology clinical units with the exception of the PAM cases who were identified in a specific Nordic constellation joint between dermatology and rheumatology. There is still no conclusively accepted clinical and/or radiographic definition of the PAM phenotype but the GRAPPA Group in 2012 undertook an ambitious attempt towards reaching a consensus (14). The clinical phenotype in the present PAM cohort is in agreement with the published consensus report.

Although HLA-B*27 has previously been associated to both PsA and PAM, strikingly in the present cohort 45% of the PAM patients had at least one HLA-B*27 allele, compared with 13% in our PsA cohort. Chandran 2013 reported that ~20% patients with PsA are positive for HLA-B*27 (23) and Alenius in a Swedish cohort (24) found that 25.7% of PsA patients were positive for HLA-B*27. Coates *et al*. recently reported that patients with PsA are 25%

HLA-B*27 positive while AS are 75% HLA-B*27 positive. They showed that patients with axial spondyloarthritis (axSpA) positive for HLA-B*27 have more severe radiographic damage as well as more marginal syndesmophytes and syndesmophyte symmetry compared to HLA-B*27 negative patients (25). For the present PAM cohort, we unfortunately lack consistent radiographic evaluation for axial disease and even if not clinically apparent, one cannot fully exclude occult axial involvement as recently described (26). Following previous and our own observations it appears that HLA-B*27 genotype is a significant biomarker for PAM.

In contrast to recent data from Coates *et al*. reporting an association between HLA-B*27 and disease severity in axial PsA and AS (25), HLA-B*27 status in our PAM cohort had no bearing on clinical and radiographic indicators of disease severity, age at disease onset or gender distribution (Table IV). This may seem surprising and one can only speculate about the role for HLA-B*27 in these different phenotypes but indicates that HLA-B*27 may not be a marker for disease severity in PAM in contrast to axial PsA (25). Rheumatology specialists confirmed the diagnosis of PsA in our cohort. Interestingly, the low HLA-B*27 frequency in our patients being recruited in dermatology settings likely mirrors a different patient selection possibly with less axial involvement compared with PsA patients recruited from rheumatology units. Thus, clinical differences between PsA patients treated in dermatology compared with rheumatology merit further studies. In conclusion, we report a high frequency of HLA-B*27 in the present PAM cohort and HLA-B*27 emerges as a valid genetic marker for PAM in PsA individuals.

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