Clinical and genetic associations of radiographic sacroiliitis and its different patterns in psoriatic arthritis

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Abstract

Objective
We aimed to 1) identify clinical and genetic associations of sacroiliitis (SI) in patients with psoriatic arthritis (PsA), and 2) describe the different radiographic patterns of SI in PsA and their clinical and genetic associations.

Methods
283 PsA patients, fulfilling CASPAR criteria, underwent detailed skin and rheumatologic assessments. In addition, HLA-B*27 and B*080101 status was recorded, which have been shown as the key genetic markers of radiographic SI in PsA. Grade 2 Unilateral or bilateral radiographic changes of SI were required for inclusion and involvement was further defined as asymmetrical or symmetrical.

Results
70 patients (25%) had radiographic SI; all either with a present or past history of backache. Regression analysis demonstrated a significant association of SI with peripheral joint erosions (p=0.043), PASI maximum (p=0.041), younger age of PsA onset (p=<0.001), presence of HLA-B*0801 (p=0.002) and only marginal significance with HLA-B*2705 (p=0.059). Asymmetrical SI was noted in 51 patients (73%). In striking contrast to those patients with symmetrical SI, patients with asymmetrical SI were more likely to be female (p=0.04), have a trend towards more severe nail disease (p=0.08) and peripheral joint erosions (p=0.08), more osteolysis (p=0.01), more HLA-B*0801 positivity (p=0.001) and much less HLA-B*270502 positivity (p=<0.001).

Conclusion
PsA developing at a younger age, severe skin disease, peripheral joint erosions, and HLA-B*0801 are significantly associated with SI, and there was only a marginal trend towards significance for HLA-B*2705. HLA-B*27 positive Axial-PsA patients resemble AS, while HLA-B*0801 positive Axial-PsA patients have asymmetrical and/or unilateral SI, which are typical of PsA.

Key words
psoriatic arthritis, HLA alleles, susceptibility, phenotype

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Introduction

Psoriatic arthritis (PsA) is a progressive, potentially destructive and disabling immune-mediated inflammatory joint disease. There are varied reports of its prevalence among patients with psoriasis (PsO), and it is becoming clear that PsA is much more common than previously thought. We have recently shown that 29% of PsO patients attending dermatology clinics had undiagnosed PsA (1). PsA is characterised by involvement of both the appendicular and axial skeleton. The question whether inflammatory axial disease and PsO represent ankylosing spondylitis with PsO, or a subset of PsA named axial PsA (AxPsA), remains a subject of debate. A number of studies have suggested that there are clinical, radiologic, and genetic differences between AxPsA and AS, suggesting that these are distinct entities (2-4). Similarly, recent studies examining typical AS-associated genetic risks in AxPsA have largely been negative, further supporting the theory that spinal involvement in PsA is genetically different from that seen in AS (5).

It is common that patients with peripheral arthritis have concomitant inflammatory axial disease, but isolated inflammatory axial disease occurs in less than 5% of PsA patients (6). The reported prevalence of axial disease in patients with PsA is quite variable (7-9). Bilateral sacroiliitis is more common in PsA than unilateral involvement (10, 11), but sacroiliitis frequently tends to be asymmetrical. Little is known about the clinical and genetic potential predictors of sacroiliitis, especially regarding the underlying patient's characteristics, and the correlation with skin disease (12-15). *HLA-B*27* is a known key genetic risk factor for idiopathic AS; however, its contribution towards the development of axial involvement in PsA remains debatable. Some studies have shown that *HLA-B*27* is an important susceptibility locus for AxPsA (12, 16-17), however, other studies, interestingly, have not agreed with these findings (18, 19). We have shown previously that 37% of PsA patients have the *HLA-B*0801* allele, which was also noted to be the

commonest susceptibility locus for the development of SI among patients with PsA (14, 20). It has been shown recently that certain HLA genes are associated with particular clinical features that collectively define the PsA phenotype of a given patient, and, importantly, that *HLA-B*27* and *HLA-B*0801* are associated with different radiographic patterns of SI in patients with PsA (21). The objectives of our study were: 1) to investigate the genetic and clinical associations of radiographic SI amongst an ethnically homogenous consecutive cohort of established PsA; and 2) to describe the different radiographic patterns of SI in PsA and their associations, if any, with clinical and genetic characteristics.

Methods

All patients who were included in both discovery and validation cohorts of our earlier genetics study were invited for prospective evaluation. In that earlier study, we performed detailed characterisation and quantification of genotypes of PsA patients belonging to a genetically relatively homogeneous population. Of 359 patients (discovery cohort=197, validation cohort=162), we were able to approach and assess 283 patients; the rest of patients either had relocated with changed personal contact details, or they died in the intervening years. All these patients (n=283) fulfilled the internationally agreed CASPAR criteria (Criteria of the ClASsification of Psoriatic ARthritis), and underwent detailed prospective evaluation with the assessors blinded to the previously reported HLA typing results and clinical data.

Following informed consent, patients underwent a detailed skin and rheumatologic assessment including disease activity measures. For skin psoriasis, the extent and severity of skin psoriasis was assessed by the Psoriasis Area and Severity Index (PASI), which is the most widely used tool for the measurement of severity of psoriasis. Moreover, we also measured body surface area (BSA) to estimate the extent of skin disease. For PsA, physical examination included recording the number of tender and swollen joints using the 68 tender/66 swollen joint counts, the

presence of dactylitis, the presence of enthesitis using Leeds enthesitis Index, as well as the number of permanently deformed joints. Clinically deformed joints were defined as the presence of fixed deformities, flail joints, fused joints, and surgically replaced joints (22). Additionally, prior usage of DMARDs, psoriatic disease requiring TNF-inhibitors (TNFi), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life questionnaire (ASQoL) were used to measure disease severity, activity and functional ability. Inflammatory markers (CRP: C-reactive protein and ESR: erythrocyte sedimentation rate) were measured; and through record review, we also documented the maximum levels of CRP and ESR ever achieved during a flare of inflammatory arthritis. Maximum ever PASI, BSA, tender joint counts and swollen joint counts were documented through extensive medical record view. In addition, an extensive medical record review was performed to obtain information regarding their previous psoriatic disease features.

A number of other patient-reported outcome measures (PROMs) were also recorded, *e.g.* Health Assessment Questionnaire (HAQ), Dermatology Life Quality Index (DLQI), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS), and radiographs were taken of involved joints along with hands, feet and sacroiliac joints. The clinical variables studied were gender, smoking habits, body mass index (BMI), units of alcohol intake per week, family history of PsO and PsA, different clinical types of PsO, psoriatic nail disease, duration of PsO and PsA, PsO and PsA age of onset, and educational attainment of the cohort. Education status was stratified by whether participants completed high school education. For the entire cohort, detailed HLA-B and HLA-C allele genotyping was determined through sequence based typing, and these results have already been published (14). The study was approved by the local Medical Research Ethics committee. There was no missing data

in this cohort (n=283), since patients were assessed in a dedicated research clinic where all above mentioned clinical, laboratory and radiographic details were collected. X-rays of SI joints were obtained prospectively on the day of assessment in research clinic.

In daily practice, PsA patients can be diagnosed as having AxPsA based on the presence of inflammatory back pain, which we believe has borderline sensitivity and specificity (23, 24). We therefore used radiographic evidence of SI to define axial disease, since this is less subjective, more reproducible and has relatively better inter-assessor agreement. Dedicated radiographic sacroiliac joint views were obtained. We defined the criteria for identifying SI if ≥ grade 2 radiographic changes were present (unilateral or bilateral). The term asymmetrical SI was assigned when grades were different between 2 SI joints, and the term unilateral SI was assigned when the opposite SI joint was completely uninvolved. All radiographs were scored by a consultant musculoskeletal radiologist blinded to any clinical characteristics and 2 trained rheumatologists.

Statistical analysis
Statistical analysis was performed using the SPSS software, v. 17. Significance was defined as $p<0.05$ (two-tailed). Baseline descriptive statistics were computed with continuous variables summarised by their means and SD; categorical variables were summarised by proportions. A chi square (X2) statistic was used to investigate the distributions of categorical variables, and continuous variables were analysed using Student's *t*-test. We applied odds ratios (OR) and associated confidence intervals (CI) to measure association between different variables. The association of different clinical variables with the diagnosis of SI was determined using univariate and multivariate logistic regressions. A logistic regression model was constructed with SI as the outcome, and those factors associated with SI on univariate analysis with significance at the 0.20 level were entered into a multivariate model. Backward stepwise multivariate logistic regres-

sion was performed with significance set at 5%, resulting in a final model. Intraclass correlation (ICC) coefficient was performed to determine inter-rater reliability of radiographic scores of SI.

Results
A consecutive cohort of 283 PsA patients [mean age 54.6±12 years; 52% female; mean PsA duration of 19±9 years; 44.5% with radiographic peripheral joint erosions; 8% with arthritis mutilans; 60% of patients requiring TNFi for PsA] was studied. Twenty-five percent (70/283) of the cohort had radiographic SI, and all patients with radiographic SI had either present or past history of backache. We could not reliably assess the presence of inflammatory back pain as per the validated criteria (Calin, Berlin and ASAS criteria) since this was a cross sectional assessment of a long-term follow up cohort and most of these patients were in clinical remission; however, the presence of back pain was documented in clinical notes of these patients with a clinical impression of inflammatory axial disease. The mean age of patients with SI was 51.8±11 years, and 54% were male. Table I compares in detail the demographics, patient characteristics, life style factors and severity of skin and joint disease in patients with SI *versus* those who had no SI. The average interrater ICC was 0.87 for sacroiliitis grade between 2 SI joints. On univariate analysis (Table II), SI was associated with longer duration of PsA ($p=0.001$), younger age of PsO and PsA onset ($p=0.003$, $p=<0.001$ respectively), and as expected, younger age ($p=0.02$), higher PASI score ($p=0.01$), presence of peripheral joint erosions ($p=0.003$), osteolysis ($p=0.003$), maximum CRP and ESR achieved during the disease course ($p=0.008$, 0.03, respectively), *HLA-B*0801* ($p=0.01$) and *HLA-B*27* ($p=0.11$). On backward step-wise multiple regression analysis (Table II), the model predicted significant association of SI with erosions (OR 1.84, $p=0.043$), PASI max (OR 1.05, $p=0.041$), younger PsA age of onset (OR 0.93, $p=<0.001$), and *HLA-B*0801* (OR 2.76, $p=0.002$). Interestingly, there was only a marginal

Table I. Descriptive characteristics of PsA patients with and without sacroiliitis.

	PsA patients with Sacroiliitis (n=70)	PsA patients without Sacroiliitis (n=213)	*p*-value
Gender – Male*	54	45	0.18
Age in years**	51.8±11	55.5±12	**0.02**
Smoking*			
Never	54	56	0.97
Ex. Smoker	34	33	
Current	11	11	
Smoking pack years**	14±10	20±21	0.16
Alcohol intake – units per week**	8.3±8.3	7.6±8	0.51
Education status*			
≤ Primary school	24	19	0.36
BMI categories*			
Normal	31	22.5	0.26
Overweight	36	36	
Obese	33	41	
Family history of PsO*	66	62	0.57
Family history of PsA*	17	17	0.96
Psoriasis types*			
Type-1	93	79	**0.010**
Type-2	7	21	
Plaque PsO*	78	80	0.76
PASI max**	7±5.8	5±5	**0.010**
BSA max**	13±15	8.7±9	**0.01**
PASI current**	2.4±3	2.0±2.6	0.23
Nail disease*	78	81	0.58
Enthesitis*	41	32	0.14
Dactylitis*	61	50	0.10
Oligoarthritis*	8.5	7	0.67
Erosions*	60	39	**0.003**
Osteolysis*	26	11	**0.002**
Arthritis Mutilans*	11	7	0.24
Deformed joints*	74	61.5	**0.052**
Number of Deformed joints**	7±9	5±7	**0.09**
PsO requiring TNFi*	17	9	**0.07**
PsA requiring TNFi*	70	55.7	**0.059**
Uveitis*	8.5	1.4	**0.003**
PsO preceding PsA*	68	65	0.56
PsA preceding PsO*	18	15	0.48
Concomitant Ps and PsO development*	13	20	0.16
PsA duration**	22.8±9.8	18±8.8	**<0.001**
PsO age of onset**	23±11	29±15	**<0.001**
PsA age of onset**	28.6±11	37±12	**<0.001**
Time from PsO to PsA development**	5.7±9	7.8±11	0.15
CRP – current**	3.1±3.1	3.2±3.2	0.76
CRP – maximum**	38±33	27±26.5	**0.006**
ESR – maximum**	36±26.6	29±22.8	**0.030**
BRAF**	14.7±4.6	14.2±5.3	0.48
HAQ**	0.56±0.52	0.58±0.58	0.79
DLQI**	2.5±3.2	2.6±4.1	0.95
HLA-B27	23	15	0.10
HLA-B0801	50	33	0.01

*figures are presented as percentage; **figures shown as mean.
BMI: body mass index; PASI: Psoriasis Area Severity Index; BSA: Body Surface Area; CRP: C-reactive protein (in mg/L); ESR: erythrocyte sedimentation rate; BRAF: Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale; HAQ: Health Assessment Questionnaire; DLQI: Dermatology Life Quality Index.

lateral involvement and the remaining 13 had unilateral SI involvement. Table III compares the demographics and key clinical features of patients with asymmetric SI *versus* those who had bilaterally symmetric SI. The asymmetric SI group were female (53% *vs*. 26%, *p*=0.04), had relatively more nail disease (86% *vs*. 68%, *p*=0.08), more osteolysis (33% *vs*. 5%, *p*=0.01), relatively more erosions (65% *vs*. 42%, *p*=0.08), more *HLA-B 0801* positivity (63% *vs*. 17%, *p*=0.001), and much less *HLA-B270502* positivity (10% *vs*. 61%, *p*=<0.001). The symmetric SI group [27% of the SI cohort, (n=19)] was more likely to be male, to have less nail disease, fewer erosions, less osteolysis, less *HLA-B*0801* and more *HLA-B*27* positivity (61% *vs*. 10%, *p*=<0.001). It was notable that although patients with asymmetrical SI had less sacroiliac radiographic damage, there was no difference in their spinal disease activity, functional ability markers (BADAI, BASFI), and spinal disease related QoL (ASQoL) measures, suggesting that they have the same intensity of symptoms and same impact.

Discussions

Different clinical and genetic factors play an important role in PsA development, which is characterised by the involvement of both appendicular and axial skeleton. In this long-term follow-up study, we have noted that one quarter of patients had radiographic SI, and SI is significantly associated not only with severe peripheral joint disease (presence of erosions) but also with severe skin disease (PASI max) along with the presence of *HLA-B*0801*. However, *HLA-B*270502* was noted to have only marginal association with SI. Contrasting clinical and genetic differences were noted among patients with symmetrical and asymmetrical SI.

The results of our study are important in a number of ways. Firstly, we have examined simultaneously in detail the association of different clinical and genetic risk factors not only with SI, but also their association with different patterns of SI (asymmetrical/symmetrical). Regarding the genetic risk factors for idiopathic AS, *HLA-B*27* is the best

trend towards significance for *HLA-B*270502* (OR 2.07, *p*=0.059) association with SI.
SI was asymmetric (unilateral or bi-

lateral involvement) in 73% (n=51) of patients. Examining those patients with asymmetric SI, we noted that 38 out of 51 (74.5%) had asymmetric bi-

Table II. Univariate and multivariate (adjusted simultaneously for variables shown) associations of different clinical and genetic variables with the development of sacroiliitis in patients with psoriatic arthritis.

	Univariate Model			Multivariate Model		
	OR*	95% CI	*p*-value	OR	95% CI	*p*-value
Age – years	0.97	0.95-0.99	0.02			
PsA duration	1.05	1.02-1.08	0.001			
PsO age of onset	0.96	0.94-0.98	0.003			
PsA age of onset	0.94	0.91-0.96	<0.001	0.93	0.91-0.96	<0.001
Erosions	2.3	1.32-3.99	0.003	1.84	1.02-3.35	0.043
Osteolysis	2.82	1.42-5.63	0.003			
PASI max	1.06	1.01-1.11	0.01	1.05	1.00-1.11	0.041
CRP max	1.01	1.00-1.02	0.008			
ESR max	1.01	1.00-1.02	0.03			
Type-2 PsO	0.29	0.11-0.77	0.01			
*HLA-B*0801*	2.02	1.17-3.51	0.01	2.76	1.46-5.19	0.002
*HLA-B*270502*	1.73	0.88-3.40	0.11	2.07	0.97-4.41	0.059

Table III. Comparison of demographics and key clinical features of patients with asymmetrical SI *versus* those who had bilaterally symmetrical SI.

	Asymmetrical SI (n=51)	Symmetrical SI (n=19)	*p*-value
Gender – Male - %	47	74	**0.04**
PsA Duration – mean	22.5 ± 10	23.5 ± 9	0.70
Plaque PsO - %	72.5	100	**0.01**
Nail disease - %	86	68	0.08
Osteolysis - %	33	5	**0.01**
Peripheral Joint Erosions - %	65	42	0.08
*HLA-B*0801 - %*	63	17	**0.001**
*HLA-B*2705 - %*	10	61	**<0.001**
BASDAI – mean	2.9 ± 2	3.02 ± 2.2	0.89
BASFI – mean	2.99 ± 2.5	3.06 ± 2.5	0.91
ASQoL – mean	5.17 ± 4.3	4.47 ± 4.24	0.54
HAQ – mean	0.53 ± 4.8	0.63 ± 0.61	0.47

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life; HAQ: Health assessment Questionnaire.

known risk factor; however, we report that *HLA-B*27* is not the predominant risk allele for the development of spinal disease in PsA. It has been shown previously that poor correlations exist between the *HLA-B*27* and the presence of clinically diagnosed sacroiliitis, limited spinal movements, disease activity measures and functional scores (17, 18). Furthermore, we note that the prevalence of *HLA-B*27* allele in PsA was 15% (14), but, the prevalence of axial disease in PsA was 25% in our series (in other studies, it ranges from 25% to >50% (7)). It is also important to note that *HLA-B*27* was only found in 23% of those with SI in our study, and in contrast, *HLA-B*08* was found in 51% of those with SI. We have also shown previously that the inheritance of *HLA B*0801* and *HLA B*270502*

are the commonest risk alleles for SI (14, 20). Now, we further extend these findings by showing that *HLA B*0801* is the only risk allele maintaining its significant association with SI, even after controlling for all known and a large number of unstudied clinical characteristics.

Furthermore, importantly, patients with asymmetrical SI have clinical and genetic features which are considered typical of PsA – more osteolysis, relatively more psoriatic nail disease and peripheral joint erosions, significantly more *HLA-B*0801*, and significantly less *HLA-B*27*. On the other hand, the group with symmetrically bilateral SI has clinical and genetic features typical of ankylosing spondylitis – more males, less nail disease, less peripheral joint erosions and osteolysis, less *HLA-*

*B*0801* positivity, and significantly more *HLA-B*2705*. Similar clinical associations of *HLA-B*27* in PsA (bilateral sacroiliitis, male gender), and its weak to non-significant association with SI has been described in literature (18, 19). These findings support the interpretation that the subset of *B*27* PsA is indeed more related to AS, despite fulfilling CASPAR criteria, while it is the *B*08* subset that exhibits the classic PsA features of axial disease described by McEwen, *et al*. (2).

Secondly, this is the first large study showing that severe skin PsO is a potential risk factor for the development of SI. We have also previously shown that severity of skin PsO can potentially be a useful clinical predictor for the development of PsA, suggesting a possible continuum of severe skin PsO as a predictor of PsA development and its extent/severity (1). Interestingly, several studies have shown that *HLA-C*06*-positive patients have more extensive skin disease but a recent study has shown that this gene is not associated with SI among patients with PsA. This differential role of HLA susceptibility genes with particular phenotypic features is intriguing. We have also recently shown that certain phenotypic features are associated with particular genes associated with PsA susceptibility and additive interactions between different susceptibility HLA alleles define the propensity for a more severe or milder musculoskeletal phenotype. We note that a recent study also suggests that moderate-severe skin PsO is more common in patients with axial PsA; however, this observation was made in only 10 patients who had axial PsA among a cohort of 166 PsA patients (25).

Thirdly, our results show that severe peripheral arthritis, defined as patients with peripheral joint erosions, is significantly more common in patients with SI, confirming a strong association between peripheral and axial joint diseases. A recent study from Toronto group has also shown that patients with damaged peripheral joints have more prevalent SI (12).

Fourthly, we have also shown that younger age at PsA onset is associated

with the development of SI. We learn from the AS literature that axial SpA continues to be active for decades, and in contrast to previous beliefs, it does not burn out overtime; rather, the majority of loss of function occurs in the first ten years from disease onset (26). A recent long-term prospective study has shown the similar pattern of worsening cervical and lumbar mobility and radiographic changes over time among patients with psoriatic spondylitis (27). This clearly underscores the importance of investigating the clinical and genetic predictors as a basis for guiding spondylitis risk assessment.

The strengths of our study include the following: (1) to investigate the clinical features of SI, we included a wide range of demographic details, clinical features, PROMs and most of disease activity indices, not only for PsA but also for PsO; (2) to minimise the selection bias, we have attempted to recruit all consecutive patients; (3) to standardise the study procedures, all patients were reviewed by a single, trained rheumatologist, and x-rays were reviewed by a musculoskeletal radiologist and 2 trained rheumatologists; (4) to our knowledge, our cohort is the largest cohort of PsA patients with such a longer duration of follow-up from one secondary care referral centre, which not only better describes the prevalence, but also its precise clinical associations. We acknowledge that there are some limitations to our study. For example, we might have been unable to capture the totality of axial manifestations since only patients with radiographic SI were included, and this was based on the following: inflammatory back pain criteria has its own limitations; most of our patients were using TNFi, which could have potentially led to under-reporting of their inflammatory back symptoms; and PsA patients generally have less pain and fewer tender joints compared to patients with rheumatoid arthritis (28), which also stress the importance of using more strict definition of axial disease. Furthermore, we acknowledge that this was a cross-sectional study, which is not the ideal study design to investigate the predictors of SI, however, this provides useful information worthy

of testing in further prospective studies. We also acknowledge that interpretation of radiographic sacroiliitis can be unreliable especially the differentiation between grades that lead to the definition of "asymmetric sacroiliitis"; however, we used a more robust approach, and radiographs were read by 3 readers, and considered only those radiographs as showing sacroiliitis that were scored positively by at least 2 readers. Further studies are needed to investigate the involvement of different components of spine, such as cervical spine disease, which has been estimated to occur more frequently than sacroiliitis (29).

In conclusion, we found that twenty five percent of PsA patients developed SI on long-term follow up. PsA developing at younger age, severe skin PsO, peripheral joint erosions, and *HLA-B*0801* are significant clinical and genetic associations of SI. Only a marginal association of *HLA-B*2705* with SI was found. We report for the first time that there are two separate principal patterns of HLA antigens explaining 2 clinically distinct sub-types of radiographic SI – asymmetrical and symmetrical, which further suggests that the genes involved in determining PsA susceptibility also specify different clinical phenotypes.

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