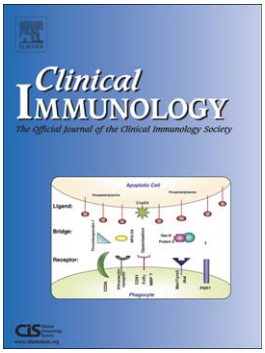

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Implications of the Diversity of Class I HLA Associations in Psoriatic Arthritis

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Abstract

We sought to validate and extend the findings of a 282 psoriatic arthritis patient cohort from Dublin using a 219 patient cohort from Bath. The central finding of this study was that several structurally unrelated HLA alleles, including *B*08:01:01, B*18:01:01, B*27:05:02, B*55:01:01* and *C*06:02:01*, were found to be significantly associated with particular phenotypic features of psoriatic arthritis, implying that the clinical diagnosis of psoriatic arthritis designates a genetically heterogeneous subset of individuals. Radiographic sacroiliitis was associated with either *B*08:01:01*, or *B*27:05:02* with implications about the role of MHC molecules in an adaptive immune response. There are implications for psoriatic arthritis diagnostic criteria since some disease features used in the criteria are under genetic control. These findings have important implications for understanding the role of MHC alleles in directing the adaptive immune response to mediate the inflammation responsible for psoriatic arthritis.

Keywords: psoriatic arthritis, genetic heterogeneity, HLA associations, phenotypic heterogeneity, adaptive immune response.

Abbreviations: Major histocompatibility complex, MHC. Human leukocyte antigen, HLA. T cell receptor, TCR. Polymerase chain reactions, PCR.

1. Introduction

1.1 Preface-The development of HLA immunogenetics In the Kunkel lab:

This paper is a part of a line of research initiated in the Kunkel laboratory. In the mid 1970's as the laboratory moved from studying the serology of the Ig system to cellular immunity, there was a broad interest of the mixed lymphocyte culture reaction (MLC) and the molecular nature of the structures responsible for stimulation and those on the T cell mediating response as part of a focus on how the T cell recognizes cognate antigen. Since the MLC response was greatly reduced in systemic lupus erythematosus when carried out in the presence of autologous serum and we had developed $(Fab')_2$ fluorescent reagents that permitted studying IgG autoantibody binding to both B and T cells, which also demonstrated the absence of cell surface IgG on B cells we could explore the binding of autoantibodies to B cells.(1) Utilizing the method of isolating T and B cells by rosetting with sheep erythrocytes, we set out to ask a question of particular interest to Henry Kunkel, whether the lupus sera were inhibiting the MLC by binding to structures on the stimulator B cells or on the responder T cells. As a control, we sought to obtain pregnancy sera that were known to inhibit the MLC response, but which lacked the then conventional anti-HLA cytotoxic reactivity assayed with mononuclear cells preparations.

Unexpectedly, these control pregnancy sera were found to contain IgG antibodies that strongly reacted in indirect immunofluorescence with a panel of B cells from different donors in a pattern that suggested they recognized MHC encoded alloantigens expressed on B cells and monocytes, but that were absent from resting T cells. (2)The question of the reactivity of lupus sera was set aside and considerable effort in the lab was then directed to characterizing the biology and genetics of the molecules identified by these normal pregnancy sera that fit in with another theme in the lab, the genetics of the C2 locus. The molecules recognized by these sera were initially termed "Ia molecules" and subsequently "HLA-DR" molecules, and represented the Kunkel lab's contribution to the description of class II MHC. This finding also explained that certain of what were termed "oncofetal antigens" identified primarily on leukemias by pregnancy alloantisera were alloantigens of the class II MHC, HLA-DR system.(2)

Application of these reagent typing sera to rheumatoid arthritis and SLE demonstrated certain HLA-DR specificities were associated with rheumatoid arthritis (DR4) and different specificities with systemic lupus (DR2, DR3), while other sera reacted across the newly identified HLA-DR specificities and recognized shared epitopes preferentially associated with a disease like

rheumatoid arthritis, which launched us (rw) on a career centered on understanding the genetics of autoimmune diseases, particularly as it concerns HLA alleles and how they influenced the development of autoimmune diseases. (3-5)

1.2. Introduction:

The spondylitis group of diseases provides an intriguing counterpoise to the predominant class II MHC associated autoimmune disease that they do not reflect the biologic function of the CD4 T cell. The pioneering identification that certain *HLA-B*27* alleles were strongly associated with ankylosing spondylitis susceptibility was the basis of this distinction, although how these alleles accomplish this is still not clearly understood.(6, 7) The fact that psoriatic arthritis and reactive arthritis/Reiter's syndrome could appear in the setting of the severe immunodeficiency of AIDS with nearly complete depletion of CD4 T cells was a tragic experiment of nature that clearly etched the conclusion that the pathogenesis of the spondylitis group of diseases was completely different from autoimmune diseases such as RA or SLE, and presumably depended on the unregulated persisting CD8 T cell clones that were highly expanded in the ultimately unsuccessful effort HIV and other secondary pathogens.(8, 9) This led to the paradigm that the genesis of the spondylitis group of diseases is the recognition by a CD8 T cell of a self-peptide presented by a class I MHC molecule, consistent with the lack of association of an autoantibody response with the diseases of this group. (8, 9)This enkindled interest in the spondylitis group of diseases and, in turn, led to a collaboration of investigators at Columbia led by Robert Winchester with Oliver FitzGerald and his colleagues in the Dublin group to use sequence-based HLA typing to study the genotype of a meticulously phenotyped cohort of Irish psoriatic arthritis patients. (10) This collaboration resulted in two major findings: The development of psoriatic arthritis was associated with several HLA alleles including *B*08:01:01, B*27:05:02, B*38:01:01, B*39:01:01* and *C*06:02:01*, while psoriasis was only associated with *C*06:02:01* and the B alleles in linkage disequilibrium with this allele. This showed that there was considerable genetic heterogeneity in psoriatic arthritis and in the psoriasis phenotype. (10) Similar results were obtained by Eder et al. (11) Certain of these alleles associated with susceptibility were then found to play a role in determining specific features of the psoriatic arthritis phenotype, etching a clear relationship between psoriatic arthritis genotype and the individual patient's phenotype.(12) Earlier, as a part of this collaboration Curren et al. showed that in psoriatic

arthritis the TCR repertoire of the T cells infiltrating sites of inflamed synovial tissue or joint fluid consisted of a striking predominance of multiple expanded CD8 T cell clones. Of particular interest in serial studies of the same patient, new oligoclonal expansions were identified, but persisting dominant clones were not observed other than one associated with the response to Epstein-Barr virus infection. (13) The significance of this shifting pluralisms among a succession of dominant clones in a site of inflammation implied that disease did not reflect aberrant behavior of a single or a few clone, but reflected the participation of a large number of functionally equivalent T cell clones distinguished by different TCR clonotypes.

However, the power to dissect the more detailed phenotypic relationships and allelic interactions was limited by the size of the Dublin cohort. We had the good fortune to join forces and establish a collaboration with the group in Bath, UK, including Neil McHugh and Deepak Jadon to form a combined Dublin-Bath cohort of 501 psoriatic arthritis patients that were all similarly phenotyped in detail and HLA-typed by a sequence-based typing approach.

In this brief paper we will focus on the implication from a limited preliminary analysis of the HLA class I alleles in the combined cohort for our conceptual understanding of psoriatic arthritis and its relation to psoriasis that is based on the identification of several different HLA genotypes that confer psoriatic arthritis and that these different genotypes are associated with different clinical phenotypes. We will summarize some univariate data on the diversity of HLA alleles that were significantly associated with particular phenotypic features identified in the conjunction of these two large psoriatic arthritis cohorts, supporting the implication that the finding of psoriasis or psoriatic arthritis does not designate a genetically homogeneous subset of individuals. Or, stated differently, that different elements in the heterogeneous psoriatic arthritis phenotype in different individuals develops from distinct autoimmune responses engendered by disparate MHC alleles.

2. Methods:

2.1 General: All studies were approved by the respective institutional review boards.

2.2 Patient Cohorts: Patients from two prospective psoriatic arthritis cohorts (Dublin, Ireland, n=282, and Bath, United Kingdom, n=219) were combined, resulting in a cohort of 501 psoriatic arthritis cases. Study inclusion criteria were based on a diagnosis of psoriatic arthritis fulfilling the Classification of Psoriatic Arthritis (CASPAR) criteria.(14)

2.2 The patients comprising the cohort were genotyped for HLA-B and C alleles by a Sanger sequence-based method as described (10), except that the PCR reactions were carried out using a nested two stage method(15), involving the heterozygous amplification of exon 2, intron 2, and exon 3 of *HLA–B* and *HLA–C*.). The sequences of certain amplification and sequencing primers were modified as follows: BF_mod: GGGAGGAGMRAGGGGACC; BR: GGAGGCCATCCCCGGCGAC; BS3R: TAGGAGATGGGGAAGGCTCC; CF: ARCGAGGKGCCCKCCCGGC; CR: GGAGATRGGGAAGGCTCCC; CS1F: GGAGCCGCGCAGGGAGGWG; CS7R: GGCTCCCCACTGCCCYTGG; CS9R: TGGATCTCAGACSSGGAGA; CS11F: CGGGGCCAGGKTCTCACAY. Nucleotide sequencing was performed using an ABI 3730 Genetic Analyzer with Big Dye Terminator version 1.1 software (Applied Biosystems). Allele assignment was performed using SeqScape version 2.5 software (Applied Biosystems) and libraries of alleles compiled from the current ImMunoGeneTics database. Allele designations are those recommended by the World Health Organization Nomenclature Committee, and which separates locus, allelic group and allelic type by an asterisk and colons. (16) Allele frequencies were directly enumerated.

2.3 Statistical analysis: Associations of alleles with disease traits were explored in multivariable logistic regression models adjusting for potentially confounding characteristics, as described. (12) Positive or negative HLA associations that were significantly contributory to the multivariable models were identified.

3.0 *Results:*

3.1 Demographics: Table 1 summarizes the demographic and certain of the clinical characteristics of the patients in the combined Dublin and Bath psoriatic arthritis cohort. The mean duration of psoriasis and psoriatic arthritis respectively are 26 and 18 years indicating reasonably adequate ascertainment of the features of the disease phenotype. Nail disease and dactylitis, elements of the CASPAR criteria, were present in a mean of 74% and 48%. Enthesitis was present in 39%, erosions in 55% and osteolysis in 15%. 24 % had radiographic evidence of sacroilitis, and was classified as symmetric in 9% and asymmetric in 15%.

3.2 HLA Associations: Table II summarizes the pattern of unweighted associations of certain HLA associations that were significantly positively or negatively contributory to multivariable models of certain phenotypic features in the combined cohort. Non-contributory alleles were omitted from the multivariable models. The striking feature is that there is a complex and distinct pattern of positive and negative / protective associations for each allele that does not exhibit notable parallels between any pair of alleles. For example, from the perspective of features distinguishing the psoriatic arthritis patients, the presence of a positive family history is separately associated with *HLA-C*06:02:01* and *B*37:01:01*, which are found together on the same ancestral haplotype, while B*18:01:01 is negatively associated with a family history of psoriasis. The onset of psoriasis before age 18 is associated with *C*06:02:01*, indicating that all of the other haplotypes bearing *C*06:02:01*, such as those containing B*57:01:01 or B*13:01:01 are equivalently associated with this feature. *B*55:01:01* is similarly associated with the onset of psoriasis before age 18, while *B*27:05:02* is protective for early onset psoriasis.

Since the length of the interval between the onset of psoriasis was found to be a quantitative trait influenced by HLA susceptibility alleles (10) the development of arthritis before psoriasis is reflected by a positive association with *B*27:05:02*, and a negative association with *C*06:02:01*. Nail disease was positively associated with the inheritance of *B*08:01:01* and *B*18:01:01*, while *B*39:01:01* and *C*06:02:01* was protective. Dactylitis and symmetric sacroiliitis mirror the same dichotomous association with *B*27:05:02* associated with the presence of these features and *C*06:02:01* with protection against these features. In contrast asymmetric sacroiliitis was associated with a different spectrum of HLA alleles from that of symmetric sacroiliitis, including *B*08:01:01, B*38:01:01* and *B*55:01:01*.

From the perspective of the phenotype conferred by an HLA allele, Table 2 shows HLA-*C*06:02:01* PsA patients were more likely to have a positive family history, early onset psoriasis, develop psoriatic arthritis after the onset of psoriasis, and were less likely to have nail disease, dactylitis and symmetric sacroiliitis. Whereas *HLA-B*27:05:02* patients were more likely to have later onset skin disease with psoriatic arthritis developing before or coincidently with milder skin involvement. They were more likely to exhibit dactylitis and symmetric sacroiliitis. A *HLA-B*08:01:01* patient was more likely to have nail disease, a current high PASI score, and asymmetric sacroiliitis. While a *HLA-B*55:01:01* patient resembles those with *C*06:02:01*, in having early onset psoriasis, and to be protected against developing arthritis before psoriatic arthritis, but the *B*55:01:01* patient differs from that genotype in being more likely to exhibit enthesitis and asymmetrical sacroiliitis.

4. Discussion:

The central finding of this preliminary analysis was that a group of structurally unrelated HLA alleles, *B*08:01:01, B*27:05:02, B*55:01:01, B*18:01:01* and *C*06:02:01*, as well as additional alleles, were found to be significantly associated with particular phenotypic features of psoriatic arthritis in the combined Dublin-Bath cohort. This supports and extends the earlier conclusions that the clinical diagnosis of psoriatic arthritis designates a genetically heterogeneous subset of individuals and that to a certain extent an individual's genotype predicts which of the heterogeneous phenotypic features of psoriatic arthritis they will manifest.(12, 17) Although the analysis of this cohort is still ongoing, these preliminary findings have implications for both the diagnostic criteria for psoriatic arthritis and for understanding the role of MHC alleles and the adaptive immune response in the disease.

Concerning the possible impact of these data on the generality of diagnostic/classification criteria should be noted is that nail disease and dactylitis, both elements of the CASPAR psoriatic arthritis criteria (14), and present respectively in a mean of 74% and 48% patients in the cohort, were associated with HLA alleles that differ in frequency in different populations. Nail disease was positively associated with *B*08:01:01* and *B*18:01:01*, and negatively associated with *B*39:01:01*, and *C*06:02:01*. Dactylitis was positively associated with *B*27:05:02* and negatively associated with *C*06:02:01*. This association between genotype and a phenotypic trait used in diagnostic criteria raises the potential that individuals of *C*06:02:01* genotype potentially might be underrepresented in psoriatic arthritis series based on the CASPAR criteria because they exhibit a phenotype of psoriatic arthritis less likely to exhibit nail disease or dactylitis. Since *C*06:02:01* is the predominant genetic determinant of psoriasis, this might result in underestimation of the frequency of psoriatic arthritis by CASPAR criteria in psoriasis cohorts where *C*06:02:01* is the dominant susceptibility genotype. Furthermore, the frequencies of these alleles differ across various populations and this may also impact the ascertainment of psoriatic arthritis in different populations.

Intriguingly in the combined psoriatic arthritis cohort, both *B*27:05:02* and *B*08:01:01* were associated with axial disease of psoriatic arthritis, as reflected by the subphenotype of radiographically demonstrable sacroiliitis, as initially reported by Haroon, et al.(12) Sacroiliitis in *B*08:01:01* individuals, except in its very interesting pattern of asymmetric distribution, is otherwise clinically and radiographically equivalent to that seen in *B*27:05:02* patients, suggesting that these different alleles are responsible for a clinically similar appearing

inflammatory process. One explanation of the association of certain *HLA-B*27* alleles with ankylosing spondylitis is focused on certain physical-chemical characteristics of the HLA-B*27 molecule, recently summarized by Powis and Colbert. (18) These include slower folding of the newly synthesized B*27 alpha chain in the endoplasmic reticulum, resulting in the formation of disulfide-linked dimers and triggering an unfolded protein response in the endoplasmic reticulum. The HLA*B27 molecule also tends to unfold on the cell surface, forming free alpha chains that can be recognized by receptors, most notably KIR3DL2. These events are linked to the IL-23–IL-17 axis through increases in IL-23 production by the unfolded protein response and triggering of the Th17 T cells that express KIR3DL2, see (18).

However, it is difficult to reconcile the current data of the equivalent *HLA B*08:01:01* and *B*27:05:02* associations in psoriatic arthritis patients with sacroiliitis with the hypothesized role of unique physical chemical features of the B*27:05:02 molecule in the development of sacroiliitis in psoriatic arthritis, since B*27:05:02 differs considerably in a number of structural features from B*08:01:01. Yet both alleles are associated with sacroiliitis in psoriatic arthritis. Accordingly, the dual HLA associations of sacroiliitis suggest that in psoriatic arthritis and perhaps other members of the spondylitis family, axial disease is not primarily a reflection of aberrant physical chemistry of a particular allomorph that triggers innate immune effector pathways, but reflect diverse canonical immune recognition processes intrinsic to the function of the MHC molecule in the adaptive immune system. These processes involve selection of a T cell clone on a self-peptide presented in the particular MHC allelomorph associated with psoriatic arthritis and subsequent activation and expansion of that clone in a reaction, not likely initiated by but ultimately driven by the same or analogous self-peptides. This view is also consistent with the evidence of canonical peptide presenting function of B*27 molecules indicated by the structural differences present in the P9 peptide binding pockets in the B*27 alellomorphs that are not associated with ankylosing spondylitis and which are characterized by a strong preferential binding of different peptides from those bound by B*27:05:02. Moreover, the finding in genomewide scan of ankylosing spondylitis polymorphisms that ERAP alleles are associated with susceptibility (19) adds support for a role of canonical peptide presentation in the development of spondylitis.

We interpret the multiplicity of different HLA class I alleles associated with clinical subphenotypes of psoriatic arthritis identified in this study as further evidence of the physiologic function of the MHC molecules encoded by these alleles in an untoward response of the

adaptive immune system in an autoimmune attack that mediates the disease manifestations. The adaptive immune system normally functions as a defense against pathogens, and ultimately the form and function of the TCR-peptide-MHC interaction reflects selective pressures that increase the efficiency of the response to pathogens. The clearest consequence of pathogen drive has been first to increase the different kinds of peptides that can bind MHC molecules by the remarkable diversification of HLA alleles, and second to allow degeneracy in peptide binding to the various MHC motifs. The somatic diversification mechanism of diversity develops a vast repertoire of clonally specific TCR structures that are selected in the thymus for their ability to recognize certain self-peptides bound to self-MHC molecules at an intermediate affinity. Notably, this degeneracy is not limited to MHC peptide binding, since increasingly evidence shows that a single TCR can bind to multiple peptides, some quite disparate in primary structure. This enables a given clone to be triggered by multiple peptides, i.e. cross-reactions, see (20). This TCR degeneracy in peptide-MHC binding enhances the ability of the T cell clones of the adaptive immune system to respond to pathogens, since it exponentially increases their ability to respond to different pathogen peptides.

However valuable in the recognition the diversity of pathogen peptides, the inherent risk for autoimmunity that underlies the selection based on the binding of self-peptides is further increased by this type of degeneracy, or cross reactivity where a TCR recognizes structurally related peptides that may differ considerably in primary sequence from the autoantigen. This provides a mechanism to explain how an autoimmune response is initiated, as was first clearly demonstrated experimentally by Wucherpfennig et al.(21) Taken together these features emphasize that potential promiscuity of each of the elements of the trimolecular interaction between MHC molecule, peptide ligand and TCR likely contribute to the inappropriate activation of a T cell clone selected on and directed to a self peptide, and highlight the challenge faced by regulatory T cell subsets and other mechanisms of peripheral tolerance to control these potentially injurious T cell clones.

The remarkable specificity of the totality of an adaptive immune response to a pathogen, or to an autoantigen, belies the fact that the ensemble of responding clones contain multiple clones that differ considerably in their peptide recognition properties, with specificity accomplished more by the net reactivity of the ensemble of responding clones. It also indicates that the classic concept of mimicry or cross-reactivity as a fixed feature of the totality of the autoimmune response in a a disease is not correct, but that at the level of a singular clone, a

clonally specific recognition of cross-reactive peptides contributes to an autoimmune disease. Accordingly, the prior exposure to a variety of trivial pathogen peptides encountered in an individual's ecosphere may stochastically increases certain memory T cells capable of recognizing self-peptides that only later contribute to the evolution of an autoimmune disease. However, the results of Curran et al. that describe a succession of different immunodominant clones in the psoriatic joint(13) is consistent with these mechanisms since it likely indicates that the same self peptide presented by the same MHC class I molecule is recognized by a variety different TCR clonotypes, and that although a given clone may undergo exhaustion and be supplanted by another clone, it is driven by the same peptide-MHC complex. Indeed, the finding of a dominant clone persisting in the inflamed synovium bearing a TCR β-chain identical to that of clones responding to Epstein-Barr virally encoded proteins may be further evidence of this mechanism.

The involvement of TCR degeneracy in autoimmune disease has recently been elegantly demonstrated (20). These authors described a CD8 clone implicated in type I diabetes mellitus with a TCR that binds a sequence in the signal peptide of preproinsulin at low avidity with a limited binding footprint, likely accounting for the clone bearing this clonotypic TCR to avoid negative selection in the thymus and enter into the CD8 T cell repertoire. However, the same TCR was shown to bind to and be activated by a large number of different synthetic peptides, some analogous to pathogen peptides, with much higher affinity and a greater footprint than the presumed self-peptide responsible for its entrance, reflecting clustered interactions that provide higher binding energy. It is presumed that activation of the clone by high affinity interaction with a pathogen peptide establishes clonal expansion and memory cells that initiate or participate in the autoimmune events of type I diabetes mellitus.

Further support for the role of the TCR-peptide-MHC complex in the genesis of ankylosing spondylitis is based on x-ray crystal structures and IR spectroscopy studies of the manner in which a self-peptide from the vasoactive intestinal peptide type 1 receptor binds to each of the B*27 subtypes (22). When bound by B*27:05, this peptide was displayed in two different conformations, and additionally when studied by IR spectroscopy all of the disease-associated B*27 molecules exhibited greater conformational flexibility in peptide binding than the non–disease-associated molecules, suggesting this flexibility in binding is implicated in disease development. (22)

However, the primary basis for HLA associations with autoimmune disease, as evident in psoriatic arthritis, reflect specific peptide-binding features exhibited by the HLA molecule that are the overarching determinant of the specificity of the autoimmune response mediating the disease. We conjecture that the different class I allelomorphs identified in this study as being associated with a particular phenotypic feature of psoriatic arthritis such as dactylitis, enthesitis or sacroiliitis, each present distinct self-peptides derived from a molecule selectively expressed in cells that become the respective target of the inflammatory responses driven by particular T cell clones specific for the particular target self-peptide bound to the MHC allelomorph, but acknowledging the role of degenerate recognition. As a consequence, the presence or absence of dactylitis, enthesitis, sacroiliitis, and the other heterogeneous features of the psoriatic arthritis phenotype is a consequence of the inheritance of MHC alleles that encode molecules capable of binding peptides uniquely expressed in these structures, accounting for the distribution of inflammation predicted by a particular patient's genotype.

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Table 1

Characteristics of Combined Dublin and Bath Psoriatic Arthritis Cohort

Clinical Feature	Total n	Frequency
		n, (%)
Age	501	56 ± 12 yrs
Female, n (%)	501	236 (47)
Family history of psoriasis, n (%)	480	270 (56)
Age of onset of psoriasis	449	28.4 ± 15.0 yrs
Psoriasis duration, years	449	26.0 (19.0-36.0) yrs
PsA duration, years	490	18.0 (12.4-25.0) yrs
Years between psoriasis and PsA	449	5.8 (0-14.0) yrs
Current PASI	483	1.2 (0.2-2.8)
Nail disease, n (%)	483	359 (74)
Pitting, n (%)	483	164 (34)
Onycholysis, n (%)	483	267 (55)
Crumbling, n (%)	352	29 (8)
Enthesitis, n (%)	483	187 (39)
Dactylitis, n (%)	483	232 (48)
Sacroiliitis, n (%)	490	119 (24)
Symmetric, n (%)	490	45 (9)
Asymmetric, n (%)	490	74 (15)
Uveitis, n (%)	483	25 (5)
Erosions, n (%)	499	273 (55)
Osteolysis, n (%)	499	77 (15)
Total on TNFi, n (%)	500	259 (52)

Table 2
The Patterns of Association of Different Phenotypic Features of Psoriatic Arthritis with certain HLA Alleles

Characteristic	Positively Associated Alleles	Protective Alleles
Family History of Psoriasis	B*37:01:01; C*06:02:01	B*18:01:01
Psoriasis Before Age 18	B*55:01:01; C*06:02:01	B*27:05:02
Arthritis Before Psoriasis	B*27:05:02	B*55:01:01; C*06:02:01
Current PASI Score	B*08:01:01	B*27:05:02
Any Nail Disease	B*08:01:01; B*18:01:01	B*39:01:01; C*06:02:01
Enthesitis	B*18:01:01; B*55:01:01; B*57:01:01	
Dactylitis	B*27:05:02	B*13:02:01; C*06:02:01
Symmetric Sacroiliitis	B*27:05:02	C*06:02:01
Asymmetric Sacroiliitis	B*08:01:01; B*38:01:01; B*55:01:01	

Highlights

- Several structurally unrelated HLA alleles, including *B*08:01:01, B*18:01:01, B*27:05:02, B*55:01:01* and *C*06:02:01*, were significantly associated with particular features within the heterogeneous phenotype of psoriatic arthritis.
- The association of radiographic sacroiliitis in psoriatic arthritis with both *B*08:01:01*, and *B*27:05:02* has bearing on whether it is driven by distinctive physicochemical features of the susceptibility molecule or on the role of MHC molecules in an adaptive immune response.
- The general applicability of psoriatic arthritis diagnostic criteria may be influenced by the genotypic association of features such as dactylitis and nail disease, used in these criteria.
- The multiplicity of associations with different HLA class I alleles have implications for understanding the role of MHC alleles and the adaptive immune response in the autoimmune response mediating psoriatic arthritis