

Psoriatic Arthritis – Separating Aetiological Factors from Those Contributing to Psoriasis and Inflammatory Arthritis

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Abstract

Psoriatic arthritis (PsA) is a complex disease with a substantial genetic component, likely to be higher than that of either rheumatoid arthritis or psoriasis. A number of genetic studies have been undertaken and suggest that the genetic factors contributing to psoriasis in patients with PsA are the same as those that are associated with psoriasis alone. Conversely, genetic factors associated with susceptibility to rheumatoid arthritis do not appear to be associated with PsA susceptibility, although only protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) and *HLA-DRB1* have been extensively investigated. Although candidate gene studies have highlighted the *-857TNF* promoter polymorphism as a potential unique PsA susceptibility gene, this finding awaits confirmation. In this article, we argue that a genome-wide association study would be the best way to identify unique PsA genetic susceptibility factors and help to understand the similarities and differences between PsA, psoriasis and inflammatory arthritis.

Keywords

Psoriasis, arthritis, gene, association, psoriatic

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Psoriatic arthritis (PsA) is commonly defined as “an inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor”;¹ however, this definition is broad and lacks specificity. As such, epidemiological and genetic studies into PsA have been limited compared with those investigating rheumatoid arthritis (RA), for example. The problem is that, while most rheumatologists recognise the clinical entity of PsA, devising criteria that reliably differentiate RA, ankylosing spondylitis or osteoarthritis with coincidental psoriasis from PsA has proved challenging. The recent publication of the Classification for Psoriatic Arthritis (CASPAR) criteria has, at last, produced an internationally recognised classification system that should facilitate further research by reducing heterogeneity within the patient groups studied.² This is of vital importance when trying to understand the aetiology of disease in order to develop targeted therapies or develop prognostic indicators.

A Disease within a Disease

Related diseases may have overlapping aetiological factors. For example, smoking has been shown to contribute to a number of inflammatory and autoimmune diseases including both RA and psoriasis.^{3,4} However, there are likely to be other factors, either genetic or environmental, that determine the features unique to each disease. The difficulty in investigating such factors in PsA is that it not only shows clinical overlap with other arthritic diseases (particularly RA), but also that the skin phenotype, psoriasis vulgaris (PsV), is a disease in its own right. Separating susceptibility factors that contribute primarily to psoriasis from those that contribute to PsA is difficult, as a patient may have psoriasis for many years before developing PsA; therefore, even if psoriasis patients have been investigated for

co-existing arthritis, the possibility that they will develop PsA cannot be excluded. A further layer of complexity is that there is a bi-modal pattern of presentation of psoriasis and different susceptibility factors appear to contribute to the different types of psoriasis. For example, type 1 psoriasis has an onset at ≤ 40 years of age and shows strong association with the human leucocyte antigen (*HLA*)-*CW*06* variant, whereas type 2 psoriasis onset (at >40 years of age) does not.⁵ Therefore, in order to separate susceptibility factors in PsA and psoriasis, the type of psoriasis should be taken into account. Despite these difficulties, progress is being made in understanding the aetiology of PsA. This article will focus on genetic investigations, as this is where most advances have occurred to date.

Evidence for a Genetic Component to Susceptibility

The evidence for a strong genetic component to PsA is now overwhelming. Family studies in different populations have consistently estimated the sibling recurrence risk to be 40–55.^{1,6,7} This compares with RA and psoriasis, where the equivalent estimates are 2–11 and 4–6, respectively.^{8–10} An elegant study of familial recurrence rates from an Icelandic population using the extensive genealogical data available there showed that first-degree relatives were at nearly 40-fold increased risk of disease, second-degree relatives were at over 12-fold increased risk and third-degree relatives had a nearly four-fold increased risk.¹¹ This decrease in risk is consistent with a cumulative effect, i.e. multiple genes contributing to susceptibility, as is the case in most other complex diseases. It supports the idea that well-designed genetic studies of PsA are likely to be rewarding in identifying novel susceptibility variants.

Separating Psoriatic Arthritis from Rheumatoid Arthritis

The shared epitope, a group of alleles of the *HLA-DRB1* gene encoding a common amino acid sequence, is the factor that confers the greatest genetic risk of RA development.¹² Several previous small studies have suggested that it may also be associated with PsA susceptibility or severity (reviewed in reference 13). However, in the largest study to date, no evidence of an association with PsA susceptibility was detected when 467 PsA patients were compared with 537 controls.¹³

Similarly, a single variant within the *PTPN22* gene is associated with a variety of autoimmune diseases, including RA, type 1 diabetes, autoimmune thyroid disease and juvenile idiopathic arthritis (reviewed in reference 14). However, several previous studies have shown no consistent evidence for an association with PsA as a whole,^{15–17} although one report suggested that it may be a susceptibility factor in males.¹⁷ These genetic findings confirm the clinical impression and epidemiological evidence that PsA is not simply an overlap of RA and psoriasis, but rather a disease in its own right. Enormous progress has been made in identifying further RA susceptibility factors as a result of both genome-wide association (GWA) studies and candidate-gene investigations. Confirmed RA susceptibility loci include the *STAT4* gene, the *TRAF1/C5* and the chromosome 6q23 genetic regions.^{18–24} To our knowledge, these have not yet been investigated for a role in susceptibility to PsA, but it can be hypothesised that there may be some overlap in susceptibility genes as both RA and PsA share the clinical feature of inflammatory joint disease.

Disentangling Psoriatic Arthritis from Psoriasis

The major genetic susceptibility locus for type 1 psoriasis is the *HLA-Cw*06* allele. Compared with controls, the allele is also associated with PsA in patients with type 1 psoriasis, but with a smaller effect size, suggesting that the primary association is with psoriasis and that there is no additional contribution to the development of arthritis in patients with type 1 psoriasis.¹³ If it were possible to identify enough patients with the rare PsA sine psoriasis, we would predict that no association with the *HLA-Cw*06* allele would be observed. Two other psoriasis susceptibility loci have been recently identified: the interleukin (*IL*)-*12B* and *IL-23R* genes both encode proteins important in T-cell development and both have shown association with psoriasis susceptibility independently of each other.²⁵ Again, investigation in PsA cohorts suggests that the primary association is with psoriasis.²⁶ For example, in a study of 520 PsA cases and over 2,000 controls, two variants of the *IL-23R* gene were associated with PsA susceptibility (rs7530511: odds ratio [OR] TT versus others = 1.27, 95% confidence interval [CI] 0.99–1.64; rs11209026: OR GG versus others = 1.40, 95% CI 1.01–1.96), but the association was stronger in patients with type 1 psoriasis without arthritis (rs7530511 OR 4.8; rs11209026 OR 2).²⁷ These studies seem to confirm that the psoriasis that occurs in PsA does not differ genetically from the psoriasis seen by dermatologists and has important implications supporting the inclusion of patients with PsA in studies investigating genetic susceptibility to psoriasis.

Unique Psoriatic Arthritis Susceptibility Factors Arising from Candidate Gene Studies

The approaches outlined above are limited to confirming overlap or distinguishing differences between confirmed susceptibility loci in other diseases and PsA. Neither strategy will identify unique PsA susceptibility factors, but it is the unique factors that are likely to give

the most interesting insights into the disease pathogenesis. Currently, candidate gene studies remain the mainstay of investigating unique PsA susceptibility loci.

Tumour Necrosis Factor

The therapeutic benefit of tumour necrosis factor (TNF)-blocking in PsA has contributed to an increased interest in TNF-promoter polymorphisms as potential disease-susceptibility factors. Thus, single nucleotide polymorphisms (SNPs) of the TNF gene at positions -238 and -308 had earlier been associated with PsV and PsA.²⁸ However, a strong linkage disequilibrium (LD) at 6p21 – a chromosomal region known to harbour also other risk factors for psoriasis (PSORS1, e.g. *HLA-CW*06*) than SNPs of the TNF gene – renders the interpretation of the respective

Separating susceptibility factors that contribute primarily to psoriasis from those that contribute to psoriatic arthritis is difficult.

findings difficult. A recent study on large cohorts of patients (PsA n=376, PsV n= 375, healthy controls n=376) revealed a strong association with the allele *TNF*-857T* (OR = 1.956; p≤0.0025) independent of PSORS1 for PsA, but not for PsV.²⁸ Therefore, the functional SNP *TNF*-857T* may represent a more specific and independent risk factor for PsA contrast than the earlier reported association with *TNF*-238A*, which seems to primarily reflect LD with PSORS1. However, further validation by a sufficiently powered replication study is required to prove that the PsA association of *TNF*-857T* is a true finding.

Vascular Endothelial Growth Factor

It has been hypothesised that abnormal angiogenesis may play a role in the aetiology of PsA. In a study of nine SNPs mapping to four candidate genes involved in angiogenesis, association to one SNP mapping to the VEGF gene was reported to be more common in 258 PsA cases and 154 controls.²⁹ Validation of this finding in a separate data set is awaited.

IL-1 Gene Cluster

IL-1 is a major inflammatory cytokine, and polymorphisms in the genes encoding several members of the *IL-1* family mapping to chromosome 2q have previously been reported to be associated with both RA and ankylosing spondylitis.^{30,31} Given the overlap of these conditions with PsA, the *IL-1* gene cluster is a good candidate for investigation. In a study of 29 SNPs across the region in 212 PsA patients and 150 controls, independent haplotypic associations were observed at the *IL-1A* and the *IL-1B-IL-1F10* regions, but, again, replication of these findings in a validation cohort is required.³²

The Way Forward – Genome-wide Association Studies and Collaboration

The investigation of genetic susceptibility variants for PsA has lagged behind that of other diseases because of the difficulties with phenotype classification and the difficulty of separating unique PsA susceptibility variants from those contributing to the overlapping constituent diseases of inflammatory arthritis and psoriasis.

However, we are now ideally placed to learn the lessons from studies in other complex diseases. The first lesson is that of the importance of large sample sizes. Previous work has shown that the biggest reason for non-replication of reported findings of association in the literature occurred when the sample size in which the association was first reported was small.³³ We are learning that most of the genetic effects in complex diseases confer effect sizes in the order of 1.2 (i.e. a 20% increased risk of disease) or less, and the ability to detect such effects requires extremely large cohorts.¹²

The second lesson relates partly to the first and concerns the importance of collaboration. The large sample sizes required to investigate susceptibility to many complex diseases have only been achieved by the pooling of sample resources. However, the importance of collaborating extends beyond basic sample collection, and many of the most successful studies have involved co-operation between clinicians and statisticians and experts in databases and bioinformatics.¹² To this end, we have established the Psoriatic Arthritis Genetics European (PAGE) consortium to facilitate future work in the field of PsA genetics. The aim is to co-ordinate genotyping efforts so that associations detected by one group can be quickly validated by others, to develop a database to store a core set of phenotype information and to share experience and resources. To date, researchers from Germany, Ireland, Italy, Sweden and the UK who are actively involved in PsA genetic studies form the consortium, but new members with >200 PsA DNA samples (preferably with ethnically matched controls) are welcome to join.

The investigation of complex diseases has been revolutionised by the introduction of technologies and platforms that allow an investigation of genetic variants spanning the whole genome: GWA studies. The final lesson, therefore, is that hypothesis-free GWA studies have yielded more confirmed susceptibility loci for complex diseases in the past 12–18 months than the previous years of candidate gene and linkage studies. Such GWA studies remain prohibitively expensive for most research groups, but it is vital that funding bodies continue to invest in this approach as it has proved hugely successful. In RA, for example, at least 10 susceptibility genes have been confirmed (unpublished data). To date, only one GWA study in a small cohort of

patients with PsA (n=91) has been reported.³⁴ Interestingly, in that study, association to the 4q27 region, harbouring the *IL-2* and *IL-21* genes, was detected and replicated in an independent cohort of 576 PsA samples. This region has previously been reported to be associated with coeliac disease, type 1 diabetes and RA and may, therefore, represent a pan-autoimmune/pan-inflammatory disease locus.^{35,36} The Wellcome Trust in the UK has funded GWA studies in RA and, more recently, type 1 psoriasis (www.wellcome.ac.uk). A large GWA study of PsA would, therefore, provide a wonderful opportunity to determine both common and unique susceptibility factors to these diseases that overlap in their clinical phenotype, but such funding is not yet available.

Summary

The large genetic contribution to PsA suggests that a well-powered GWA study would have a high likelihood of success in identifying genetic susceptibility factors for this disabling condition. These are exciting times as there is a real possibility that we will be able to make progress in understanding the genetic basis of PsA. This is vital in terms of targeted drug development and therapy and to inform prognosis. ■



Anne Barton leads a research team within the Genetics and Genomics group of the arc Epidemiology Unit in Manchester investigating the genetic basis of rheumatic diseases. Following the award of her PhD in 2001, she received a Wellcome Advanced Fellowship to continue her work. She graduated from the University of Manchester and embarked on a career in rheumatology in 1995.



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