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Editorial

Genetic Studies of Psoriatic Arthritis: Dissecting Joints and Skin

Psoriatic arthritis (PsA) is broadly defined as "an inflammatory arthritis associated with psoriasis which is usually negative for rheumatoid factor"[1]. Such a definition has been widely criticized and no internationally agreed criteria for the diagnosis of PsA have ever been successfully developed and applied. A major point of debate remains the distinctiveness of PsA as an entity. Patients with psoriasis may coincidentally develop rheumatoid arthritis (RA), ankylosing spondylitis (AS), etc. The proportion of patients who therefore develop a distinct entity of PsA and the key features that make up this entity are still subject to much debate. Several well conducted epidemiological surveys have noted an increased prevalence of inflammatory polyarthritis in patients with psoriasis. In addition, there is an increased prevalence of psoriasis in patients with arthritis, particularly in patients who are negative for rheumatoid factor[1]. In examining for distinct clinical features, however, most studies have used patients with an established diagnosis attending hospital clinics, leading to potential bias. Community based studies investigating this question are uncommon and are limited by small numbers and short duration of followup. Harrison, *et al* found that patients with inflammatory arthritis and psoriasis were more likely to be male and to be negative for rheumatoid factor. There was also a trend toward a distal interphalangeal (DIP) joint predominant pattern being more frequent; in other respects the pattern of arthritis was similar, independent of the presence of psoriasis[2]. Similarly, van Romunde, *et al* found few differences between "psoriatic arthritis" and other forms of polyarthritis, with the exception of more frequent involvement of the DIP joints. This feature was, however, too infrequent to act as a sensitive marker for PsA[3]. Recent magnetic resonance studies have led to the proposal that PsA and the spondyloarthropathies are enthesis based diseases that are distinct from RA, where synovitis is the primary pathological feature[4]. Further investigation of this hypothesis is clearly necessary.

The controversy over the distinctiveness of PsA is important to bear in mind at all levels of research in this disorder. A distinct entity is likely to have a distinct etiology over and above the etiology of related inflammatory arthropathies that may simply coincide with psoriasis. Such factors may be genetic and/or environmental and in this editorial we consider the role of the former. Important questions that remain unanswered are whether there is a distinct genetic susceptibility to PsA over and above both (1) that which predisposes to psoriasis itself, and also (2) that which might be expected by the co-occurrence of psoriasis and other arthropathies (e.g., RA and AS).

EVIDENCE FOR GENETIC SUSCEPTIBILITY TO PsA

Twin and family studies are the classic way of investigating genetic contribution to a disease, but twin studies have not, to our knowledge, yet been undertaken in PsA. Family studies do, however, suggest that first-degree relatives are at increased risk of developing PsA[1]. The sibling recurrence risk (λs) measures the excess risk to a sibling over the general population risk and is estimated to be roughly 4 for both RA and psoriasis[5]. Moll and Wright's original family studies suggest that the λs for PsA may be significantly higher, suggesting an even stronger genetic contribution to its etiology and lending support to the notion that additional susceptibility loci exist[1]. PsA would not, however, be expected to follow a simple Mendelian trait. It is a complex disease, and the investigation of the genetic contribution is hampered by several factors. These include late age at onset, variable penetrance (not everyone with susceptibility genes will develop PsA), variable expression (different combinations of genes may predispose to different patterns of PsA), unknown gene–gene and gene–environment interactions, locus and allelic genetic heterogeneity (different genes or different alleles of the same gene may produce the same phenotype), and misclassification of clinical phenotypes. Such factors are, however, not a bar to investigation but need to be considered in any analysis.

HLA STUDIES IN PsA

The majority of studies investigating genetic susceptibility to PsA have been case-control association studies of polymorphisms in candidate genes, although not all studies have included a control group with psoriasis alone. Case-control studies of HLA have found that, although B13, DR7, HLA-B38, and B39 are all associated with PsA, the association may

be similar to those found in psoriasis alone[6]. Whether all these associations are independent or due to linkage disequilibrium across the region with the major psoriasis susceptibility locus, Cw6, and whether Cw6 is associated with PsA independently of psoriasis is not clear. By contrast, HLA-B27 appears to be associated with a subgroup of PsA patients with sacroiliitis independently of psoriasis. This antigen has also been associated with DIP joint disease, suggesting that the HLA-B27 association may not all be explained by the coincidence of AS with psoriasis[6]. Gladman, *et al* also described an independent association of PsA with B27 and B7 compared to psoriasis alone[7]. HLA-DR4 has been associated with a peripheral symmetrical arthritis, suggesting an overlap with RA susceptibility loci[6]. Few studies have investigated linkage between HLA and PsA. In 103 psoriasis affected sib-pair families linkage to 6p (HLA) was detected, but it was most significant in those families without PsA[8]. This finding has now been replicated in an independent cohort of families[9]. The whole area remains controversial and the magnitude of the contribution, if any, of HLA to PsA susceptibility over and above that which contributes to psoriasis alone still remains to be determined.

NON-HLA GENES IN PsA PATHOGENESIS

Several studies have investigated the association of PsA with non-HLA genes, with evidence that some non-HLA genes may contribute to PsA independently of psoriasis. The -238 tumor necrosis factor-α (TNF-α) promoter polymorphism has been associated with both juvenile onset psoriasis and PsA[10], while the TAP1*0101 allele was associated with psoriasis but not PsA[11]. Association of MICA (class I MHC chain-related gene A) has been reported to PsA independent of psoriasis[12]. Replication of these associations in independent data sets has not, to date, been reported. No association between low molecular protein 2 or 7 polymorphisms[13] or between T cell receptors and PsA[14] has been detected, but these studies were small with insufficient power to confidently exclude an association. Case-control association studies are subject to error, particularly due to population stratification. Cases and controls, therefore, need to be well matched to minimize this possibility. Sample size and inadequate matching of cases may explain conflicting results in some studies. For example, in an English study an association of polymorphism in the immunoglobulin heavy chain gene was found with PsA, but not psoriasis[15], but in Italian patients the reverse was found[16]. Alternative strategies include linkage analysis in affected sibling pair or multigenerational PsA families or association studies in which family based controls are used (transmission disequilibrium testing). Both approaches have the advantage of avoiding the complication of population stratification, but large scale collection of such family material can be problematic.

Evidence for a role of additional candidate genes may also be suggested from studies that compare the inflammatory process in PsA with that seen in psoriasis itself and also RA. For example, the lymphocytes responsible for inflammation in the joint appear to differ from those causing inflammation in the skin, and the homing mechanism associated with cutaneous lymphocyte antigen (CLA) appears to be relevant to the skin but not the joint inflammation[17]. Comparing RA to PsA, many of the differences appear to be quantitative rather than qualitative. PsA synovium does, however, have increased vascularity and fibrosis. E-selectin expression is also markedly reduced in PsA and, while IL-2 is absent from RA synovium, it is detectable in PsA[18].

FUTURE WORK

A well designed case-control study should have the ability and power to separate the genetics of susceptibility to PsA from those of its constituent parts. Thus studies need to be undertaken comparing PsA subjects with controls that (1) have psoriasis without arthritis, and (2) have inflammatory arthritis without psoriasis. As an example of the former, subjects and psoriasis controls should be matched for age, sex, psoriasis subtype, and geographical area to minimize problems of population stratification. They should also have had skin disease for > 10 years to minimize the numbers who will potentially yet develop PsA[19]. To detect small genetic effects large numbers of subjects in each group are required, particularly if the population frequency of the rare allele is low. Large numbers are also required to allow subgroup analysis, stratifying the PsA data set for type of psoriasis and pattern of joint involvement. Such a study, we believe, is feasible even in the absence of an agreed definition of PsA, provided adequate documentation of cases is undertaken to allow subgroup analysis. Candidate genes to be examined would include HLA and non-HLA genes, including genes associated with the differences in pathogenesis already discussed. In addition, genes implicated in RA etiology, e.g., IL-10, IL-8, and TNF-α, as well as those associated with areas of known linkage to psoriasis, e.g., 17q25, 6p, and 4q32-35[8], would also be important candidates to help distinguish the unique genetic contribution to PsA. Excessive paternal transmission has been reported in PsA, so genes that exhibit genomic imprinting would also be candidates[20]. It is only with this dual study design that the extent to which the genetic susceptibility to PsA is independent of psoriasis and other inflammatory arthropathies can be assessed.

PsA represents an interesting conundrum of a “disease within a disease.” In addition there remains continuing debate regarding what features distinguish PsA from other inflammatory arthropathies that may coincide with the presence of psoriasis. A strong genetic contribution to PsA has been noted and may be stronger than for RA or psoriasis alone. In studying the genetics of PsA it is important to control carefully for psoriasis and its known genetic factors; it is also important to study genes potentially associated with other inflammatory arthropathies. An adequately powered study to dissect skin and joints at a genetic level would be a major contribution to our understanding this complex and fascinating entity.

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