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REVIEW ARTICLE

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Genetic epidemiology of psoriatic arthritis

Abstract Psoriatic arthritis (PsA) is defined as an inflammatory arthritis (IA) associated with psoriasis and is usually negative for rheumatoid factor. This ambiguous definition has impeded research into this subject, but as yet no agreed definition or classification criteria exist for PsA. Furthermore, there are those who question whether PsA exists as a distinct disease, or is a mere coincidence of inflammatory arthritides such as rheumatoid arthritis or ankylosing spondylitis with psoriasis. The pathogenesis of both IA and psoriasis is complex, involving interactions between many different genes and environmental etiological factors. It is likely that PsA is also a complex disease. The identification of genetic susceptibility factors unique to PsA over and above those that contribute to IA or psoriasis alone would put an end to speculation as to whether PsA exists as a distinct disease. In addition, it may aid in the development of novel therapies which target PsA specifically. This review summarizes the approaches taken to identify PsA susceptibility genes, and outlines some interesting regions which may harbor PsA susceptibility genes.

Key words Genetics · Gene · Psoriatic arthritis (PsA) · Psoriasis · Review

Introduction

The word "psoriasis" is derived from the Greek word "psora" meaning itch.[1] Psoriasis is a T-cell-mediated noninfectious inflammatory dermatosis affecting 1% to 2% of the general population, with psoriasis vulgaris (plaque form) being the most common.[2] The prevalence of inflammatory arthritis (IA) has been reported to be as high as 40% amongst patients with psoriasis,[3–7] leading to the hypothesis that a distinct disease, namely psoriatic arthritis (PsA), does exist. The first case was probably described by Alibert in France in 1818, but it was not until 1964 that PsA was recognized as a distinct entity by the American College of Rheumatology.[8,9] PsA is defined as an IA associated with psoriasis which is usually negative for rheumatoid factor.[10] Using this definition, the incidence of PsA from a community-based cohort in the UK was estimated to be 3.4 per 100 000 per annum in females and 3.6 per 100 000 per annum in males, although it should be noted that the study did not include patients presenting with a monoarthritis or spondyloarthropathy.[11] Other studies have estimated the incidence of PsA to be between 6 and 8 per 100 000 per annum, and the prevalence to be between 0.1% and 1%.[10,12–15] Since both IA and psoriasis are complex diseases (i.e., they have both genetic and environmental susceptibility factors), it is expected that PsA will also be a complex disease. Some PsA susceptibility factors may be shared with IA and/or psoriasis, but others are likely to be distinct.

However, there are those who question whether PsA is truly a distinct arthropathy and not simply the coincidental occurrence of psoriasis with other types of inflammatory arthritides such as rheumatoid arthritis (RA) or ankylosing spondylitis (AS).[16] We will examine the evidence from epidemiological, clinical, and genetic studies which support the existence of PsA as a distinct disease.

Epidemiological evidence

Epidemiological studies have shown an increased prevalence of IA in patients with psoriasis. A community study in Sweden by Hellgren[17] found that 5.4% of psoriasis patients had classical, definite, and probable "RA" compared with only 0.9% of matched controls. Studies conducted amongst psoriasis patients in hospitals showed that 31% to 48% of them have clinical or radiological evidence of IA.[3–7] Similarly, studies have shown an increased prevalence of

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psoriasis in patients with IA, especially in those who are seronegative for rheumatoid factor. For example, Baker[18] showed that psoriasis was present in 1.2% of 407 seropositive RA patients compared with 20.2% of 124 patients with seronegative polyarthritis. Similarly, Hellgren[17] found that 4.5% of 661 definite, classical, or probable RA patients had psoriasis compared with 2.7% of controls, and the difference was statistically significant. In addition, Harrison et al.[11] reported that 5.3% of 966 patients with early IA from the Norfolk Arthritis Register had psoriasis, and these patients were more likely to be seronegative.

The epidemiological evidence suggests, therefore, that psoriasis and IA occur together more often than expected by chance alone, and this supports the existence of a distinct disease of PsA. If PsA is a distinct disease, then it should be possible to distinguish it from other types of IA based on clinical or other features.

Clinical evidence

The clinical evidence to support the existence of PsA as a distinct disease from RA includes the absence of rheumatoid factor and subcutaneous nodules (two diagnostic features of RA), an equal gender distribution (a ratio of 3 females to 1 male in RA), asymmetry as opposed to symmetry of joint involvement, a greater degree of axial involvement, and distal interphalangeal (DIP) joint disease.[10,19,20] Magnetic resonance imaging studies have suggested that PsA and the spondyloarthropathies are enthesis-based diseases, unlike RA which is a diseases of the synovium.[21] A number of X-ray changes have been described which are characteristic of PsA, such as a "pencil-in-cup" destructive deformity of the DIP joints due to osteolysis and resulting in digital telescoping.[22,23] Juxtaarticular osteoporosis, which is characteristic of RA, may occur early in the disease course of PsA, but studies have shown that it is transient, and normal mineralization is usually maintained despite this erosive disease.[24,25] Furthermore, periarticular osteoporosis appears to be associated with joint inflammation in RA, but not in PsA.[26]

Clinical features that distinguish PsA from AS include the fact that AS patients tend to develop the disease at an earlier age and are more likely to have inflammatory neck and back pain and stiffness.[27] In AS patients with spinal involvement, the development of syndesmophytes tends to progress from the lumbar to the cervical spine, whereas in psoriasis, this progression appears to be random.[28] In addition, AS patients are more likely to have osteitis, squaring of the vertebral bodies, and bilateral sacroiliitis.

Many clinical and radiological studies support the concept that PsA is a separate disorder and not simply the coincidence of psoriasis with different types of IA. However, most of these studies were performed in established cohorts of patients, and the X-ray changes may have influenced the selection or segregation of these patients as having PsA. For example, no radiological features or set of criteria were found to be characteristic of PsA when comparing patients with seronegative polyarthritis with psoriasis to those without psoriasis.[29] Furthermore, the asymmetry of disease in PsA compared with RA may simply reflect a quantitative rather than a qualitative difference, as the number of joints affected by arthritis in the body is finite.[30]

Hence, although the clinical data are largely supportive of the existence of PsA as a distinct disease, this may be undermined by the selection bias of the patients studied. Indeed, an overlap of clinical signs and symptoms with other forms of IA has been the largest stumbling block in the development of classification guidelines, and this can hinder all areas of research into this entity.

The identification of genetic factors uniquely associated with PsA would provide strong support for the existence of PsA as a distinct entity, but this is not a trivial task. Like all complex diseases, the pathogenesis of PsA is thought to be multifactorial, involving interactions between many genes (polygenic) and as yet unidentified environmental factors.[31,32] Not only is the disease likely to exhibit variable penetrance (not everyone with susceptibility genes will develop PsA) and variable expression (different combinations of genes may predispose to different patterns of PsA), but it is likely that there will be an overlap in the etiological factors contributing to psoriasis and PsA or IA and PsA. Dissecting out the genetic contribution to PsA therefore poses a major challenge. This review will focus on the studies reported to date which have attempted to identify PsA genetic susceptibility factors.

Genetic evidence for the existence of PsA

Twin and family studies are the classical way of demonstrating a genetic component to disease susceptibility. Although no twin studies have been undertaken as yet, family studies have shown that the first-degree relatives of patients with PsA are at increased risk of developing the disease. For example, PsA was demonstrated in 8.3% of first-degree relatives of patients with PsA.[31] The sibling recurrence risk (λs) is a measure of the excess risk to a sibling of an affected individual over and above the general population risk, and is estimated to be approximately 4 for RA and 5–10 for psoriasis.[33] Based on a family study by Moll and Wright,[34] the λs for PsA has recently been calculated to be 27. Such evidence suggests a stronger genetic contribution to the etiology of PsA than either IA or psoriasis, and lends support to the existence of PsA as a distinct entity.

In both IA and psoriasis, the major genetic susceptibility component resides within the human leucocyte antigen (*HLA*) gene region on chromosome *6p*, and there have therefore been a number of studies investigating this locus in relation to PsA susceptibility.[35–38]

PsA and the HLA region

Linkage studies have shown that the major genetic contribution to the etiology of psoriasis arises from a locus within

the major histocompatibility complex (MHC), *6p21.3*. This locus has been designated as *PSOR1*, and association studies in a number of populations have consistently demonstrated an association of psoriasis with the *HLA Cw6* allele, *HLA Cw*0602*.[39–48] In patients with PsA, the association with *HLA Cw*0602* appears less certain. It is associated with a younger age at onset of psoriasis (<40 years) in PsA patients, suggesting that the association is primarily with psoriasis.[47,49–52] Recent fine-mapping studies have localized the likely psoriasis disease gene to a region 60–100 kb telomeric of *HLA C*.[53,54] Thus *HLA C* does not appear to be the true susceptibility locus, but appears to be in linkage disequilibrium (LD) (i.e., the genes are transmitted together) with the disease locus. An Italian study of 147 psoriasis patients suggested that the corneodesmosin gene may be the disease locus.[55] However, a study from Spain involving 95 psoriasis and 74 PsA patients, whilst confirming an association to a region telomeric of *HLA C* in both psoriasis and PsA patients, found no association with the gene.[54]

Association to other HLA class I genes has also been investigated in PsA. *HLA B13*, *B17*, *B47*, *B16 (B38, B39)*, *B37*, and *B57* have all been associated with psoriasis with or without arthritis, but *HLA B13*, *B17*, *B47*, and *B57* have been reported to be in LD with *HLA C* and are therefore unlikely to contribute separate effects.[48,56–64]

Both *HLA B7* and *B27* have been shown to be associated with PsA independently of psoriasis.[52,61,65] The association of *HLA B27* with PsA is interesting. The fact that *HLA B27* has been found to be associated with the spondyloarthritic form of PsA, and is more likely to be present in PsA patients with bilateral sacroiliitis than those with unilateral sacroiliitis, may suggest that the association is primarily in patients with AS and coincidental psoriasis.[58,61,66–69] However, it has also been found to be associated with peripheral arthritis in PsA, suggesting a contribution over and above any overlap of psoriasis and AS.[70–72] Carriage of *HLA B27* has also been found to correlate with the later onset of arthritis in PsA patients.[61]

The association of *HLA B16* and its splits *B38* and *B39* is more confusing. *HLA B16* and *B39*, but not *B38*, were found to be associated with the axial arthropathy subgroup of PsA in two Italian studies involving up to 50 PsA patients,[73,74] but a larger French study with 108 PsA patients reported that *HLA B38* was strongly associated with central involvement in PsA.[67] In contrast, *HLA B38* has also been shown to be associated with peripheral arthritis in a number of PsA populations, with the largest being a Canadian study involving 158 patients.[51,61,69,75] Both *B38* and *B39* have been found to correlate with an early age of onset of psoriasis and arthritis in PsA patients.[61,75]

HLA B17 has also been investigated for an association with PsA, and was reported to correlate with a later onset of arthritis in one small study (60 PsA patients),[75] but was associated with early age at onset of arthritis in a larger series of 158 PsA patients.[61]

The association of polymorphisms in the *HLA DRB1* gene and the shared epitope (SE) (a group of DRB1 alleles associated with RA and sharing a conserved amino acid motif in the third hypervariable region of the DRβ chains) with RA are well established, and have also been investigated in PsA susceptibility studies.[38] Both *HLA DR7* and *DR4* have been reported to be associated with PsA.[56,64,68,75] *HLA DR7* was found to be in LD with *HLA Cw6* and was associated with peripheral arthritis.[58,62,64] The association of *HLA DR4*, however, appears to be confined to a subgroup of PsA patients with polyarthritis, mimicking that of RA.[56,61] A Canadian study has reported differences in *HLA DRB1* allele frequencies between *HLA DRB1*04*-positive PsA and RA patients: in patients with at least one *HLA DRB1*04* allele, *HLA DRB1*0402* was found to occur more frequently in PsA than in RA or healthy controls, whereas *HLA DRB*0401* occurred less often.[76] No difference in the frequency of carriage of SE alleles between healthy controls and PsA patients was found in a UK population.[77]

Studies of IA have shown that *HLA DRB1* is strongly associated with the development of erosions, suggesting that it may be a severity rather than a susceptibility gene.[78,79] Therefore, the role of the gene in determining the severity of PsA has also been investigated. The presence of the SE has been significantly associated with the development of erosions in a UK cohort of PsA patients.[77] In addition, *HLA DR3* and *DR4* have also been reported to be associated with severe and erosive disease in a number of PsA populations.[52,56,58] Furthermore, *HLA B17* has also been shown to be associated with a more severe disease,[58] whereas *HLA A3*, *B7*, and *B13* have been associated with a milder disease in PsA.[56,61] *HLA DR7*, on the other hand, has been associated with chronic, severe disease in a small New Zealand population (60 PsA patients), and with mild disease in a large (158 PsA patients) Canadian cohort.[58,61] One explanation for this apparent contradiction is that *HLA B22* and *DQw3* in the presence of *HLA DR7* provide "protection" from disease progression in PsA, but in the absence of *HLA DR7*, *DQw3* predisposes the patient to an increased risk of disease progression. In addition, *HLA B27* in the presence of *HLA DR7* may confer susceptibility to disease progression in PsA patients.[80]

In summary, there have been a large number of studies examining possible associations of *HLA* genes with PsA. The results often appear conflicting, and there are several reasons why this may occur. Firstly and most importantly, it is established that HLA alleles occur at differing frequencies in different ethnic populations, and therefore this may account for the variation in the associations observed across populations.[62,81] Secondly, *HLA* may be associated with severity rather than susceptibility. If cohorts differ in terms of disease severity, this may explain some of the conflicting associations reported. Thirdly, some *HLA* associations may only be observed in the presence of other interacting genes, which may not yet have been identified. Finally, many of these studies have used small sample sizes. It is often difficult to separate psoriasis and IA susceptibility factors from those of PsA because these control groups have not been included in many of the studies. Overall, however, *HLA* does not appear to make a significant contribution to PsA disease development as it does with IA and psoriasis, and the challenge now is to identify *non-HLA* susceptibility genes.

PsA and the non-HLA genes in the MHC region

Other MHC genes, in addition to or instead of the classic *HLA*, may also harbor a major susceptibility locus for PsA, as appears to be the case for IA and psoriasis.[38,82] One gene that has been investigated is tumor necrosis factor *(TNF)α*, because it is a pivotal proinflammatory cytokine and immunoregulator produced by monocytes/macrophages. The *TNFα* gene is encoded in the HLA class III region of chromosome *6*, centromeric to *HLA B* and telomeric to *HLA D*. Polymorphisms in the promoter region of the *TNFα* region are of considerable interest because they may alter the levels of TNFα production, and increased levels of TNFα have been reported in psoriasis skin, synovial fluid, and the synovium of PsA patients.[83–85] In addition, TNFα has been detected in inflamed enthesis, and TNFα blockade has been used successfully in treating PsA patients.[86,87] A number of promoter single nucleotide polymorphisms (SNPs) have been described and tested for association with PsA. A *TNFα* promoter SNP at position *-238* was shown to be associated with PsA in a German population comprising 62 PsA patients, and this has been replicated in a UK study (124 PsA patients), but the *TNFα-238A* allele was found to be in LD with the *HLA Cw*0602* allele, suggesting that the primary association may be with psoriasis.[49,88] In contrast, the *TNFα-308* promoter SNP and a haplotype of microsatellite alleles spanning the *TNFα* locus have both been associated with PsA independently of psoriasis.[89] Recently, association with 5 *TNFα* promoter polymorphisms has been investigated in 143 UK PsA patients, and an association has been detected to both the *TNFα-238* and *-1031* SNPs. Haplotype analysis of all 5 SNPs revealed a significant association to 2 haplotypes.[90] However, no association with *TNFα* polymorphisms was found in small Japanese (20 and 37 PsA patients) and Jewish (52 PsA patients) studies.[62,91,92] These apparently conflicting results may be explained if the gene is associated with severity of, rather than susceptibility to, PsA. In support of this, an Irish study with 147 PsA patients showed the *TNFα-308* promoter polymorphism was associated with the presence of erosive change in PsA patients.[93]

Other genes that have been investigated as candidate PsA susceptibility genes include the major histocompatibility complex class I-related gene A (*MICA*). A trinucleotide repeat polymorphism, *MICA-A9*, has been reported to be associated with PsA independently of *HLA Cw*0602* and psoriasis in a Spanish population.[94] *MICA* is located 47 kb upstream from the *HLA B* gene, and is a transmembrane protein mainly expressed in epithelial cells of the intestine. It is thought to play a role in the innate defense system. In addition, *MICA-A9* was found to be in LD with *HLA B57* and *B38*, *TNFα*, and *HLA-DRB1*, suggesting that the *MICA* gene or one nearby may be the true PsA disease locus, and that reported associations with other genes are due to the LD in the region.[95] This association has recently been replicated in a Jewish PsA cohort, suggesting that the association is real.[62]

Low molecular weight protein (*LMP*) *2* and *7* are two MHC-encoded proteasome subunits which influence the endopeptidase activity of a multicatalytic protein complex involved in the degradation of cytosolic peptides in association with MHC class I molecules. *LMP2* polymorphism has been found to be associated with acute anterior uveitis and peripheral arthritis in *HLA B27*-negative and -positive AS patients.[96,97] However, no association was found between *LMP2* and *7* gene polymorphisms and patients with PsA.[98]

Another interesting candidate PsA susceptibility gene mapping to the HLA gene region is the transporter associated with antigen processing (*TAP*) gene. Antigenic peptides attached to HLA class I molecules are degraded from cytosolic proteins, assembled with HLA molecules, and then transported to the cell surface. These peptides are actively transported across the endoplasmic reticulum membrane by TAP. The *TAP* gene consists of *TAP1* and *2* genes encoding a heterodimer molecule which forms a heterodimeric complex delivering antigenic peptides to the endoplasmic reticulum prior to the assembly of class I molecules.[99–101] The *TAP1*B* (0201) allele has been associated with AS, especially in patients with extraspinal disease, and therefore the gene was thought to be a strong candidate PsA susceptibility gene.[102,103] However, the *TAP1*A* (0101) allele was found to be associated with juvenile-onset psoriasis but not with PsA.[104]

Hence, several *non-HLA* genes mapping within the MHC region have been investigated for an association with PsA. Association to *TNF* and *MICA* have been replicated in independent data sets, and these associations appear to be independent of psoriasis. However, in none of the studies was an IA control group included, so it remains unclear whether these are unique PsA susceptibility factors. As in IA and psoriasis, there are likely to exist a number of susceptibility genes that reside outside the MHC region, and several studies have attempted to identify these.

PsA and the non-HLA regions outside the MHC region

The majority of studies have focused on investigating genes thought to be good candidate PsA susceptibility genes either because they have been associated with IA and/or psoriasis, or because of knowledge of biological pathways. For example, as both psoriasis and IA are thought to be T cell-mediated diseases, the T cell receptor (*TCR*) gene has been investigated as a candidate PsA susceptibility gene. However, no association was detected.[64] Similarly, the immunoglobulin heavy-chain genes on chromosome 14 have been investigated, and an association with PsA was reported in a UK study of 28 PsA patients. However, the same group found no association in an Italian cohort of 55 PsA patients.[105,106]

Interleukin (IL) 1 is a cytokine secreted by monocytes and macrophages, and its biological effects are controlled by a number of interacting receptors and antagonists. The genes encoding *IL-1α*, *IL-1β*, *IL-1R1*, and *IL-1ra* loci are located as a cluster on chromosome *2q12–13*.[107] The

IL-1α-899 C allele has been found at higher frequencies in PsA patients compared with healthy controls.[108] Another study showed an association between *IL-Ira* gene polymorphism and early onset psoriasis.[109]

Another gene that has been investigated is the caspase activating recruitment domain (*CARD*) *15* or nucleotide oligomerization domain (*NOD*) *2* gene, which encodes a protein involved in the interaction with bacterial lipopolysaccharides, the induction of apoptosis, and the activation of the nuclear factor-kappa-B (NF-κB) signaling pathway. NF-κB regulates the transcription of many proinflammatory and immune-related genes.[110–112] Polymorphisms of the *CARD15* gene have been shown to be causal in the etiology of Crohn's disease.[113,114] Since the frequency of both psoriasis and PsA is increased in Crohn's disease patients, the causal polymorphisms have also been tested for association in these patient groups. An association between *CARD15* and psoriasis has been excluded in North American, Italian, and UK cohorts.[115–117] However, recently an association between *CARD15* and PsA has been reported from Newfoundland, Canada, in a series of 187 PsA patients and 136 healthy controls (odds ratio 2.97 (95% confidence interval 1.61–5.47)).[118] This finding requires replication in other data sets.

Association studies to date have shown some conflicting results on the genes involved in the etiology of PsA. There are a number of possible explanations for this. Firstly, because positive association studies are more likely to be published than negative ones, it has been estimated that many of the reported associations could be spurious due to publication bias.[119] Secondly, studies are often underpowered with small sample sizes and therefore lack the power to confidently exclude any association. Thirdly, there is rarely any attempt to replicate findings in independent data sets, and fourthly, these discrepancies may reflect the different ethnic backgrounds of the populations being studied.

Linkage studies

An alternative approach to identify susceptibility genes is to perform whole genome scan (WGS) linkage studies to identify regions of the genome likely to harbor PsA susceptibility genes. This would increase the prior probability of detecting an association with genes mapping within regions of linkage. The main drawback of the WGS approach is that until recently, large collections of families with PsA were not available. Some researchers have attempted to overcome this by investigating linkages in families with psoriasis and then stratifying these families by the presence of joint complaints, although a formal diagnosis of PsA was not made. Using this approach, the strength of the evidence for linkage to chromosomes *3q*, *4q*, *5q*, *17q,* and *15p* was increased in psoriasis families with joint complaints, suggesting that these regions may harbor PsA susceptibility genes (Fig. 1).[45] It is interesting to note that all these regions have also shown linkage in RA families.[38]

Another way of prioritizing regions that may harbor PsA susceptibility genes is to identify loci that overlap between linkage studies of RA, AS, and psoriasis. We have analyzed data from WGS linkage screens published in RA, AS, and psoriasis families.[35–38,82] Regions were defined as showing overlap if they had been detected in at least two WGSs of psoriasis and one RA WGS, two psoriasis WGSs and one AS WGS, one psoriasis WGS and two RA WGSs, or one psoriasis, one AS, and one RA WGS (Fig. 1). The regions identified include chromosomes *1p*, *2p*, *6p*, *16q*, *10q*, *17q,* and *20p*. Within these regions, there are a number of interesting PsA candidate genes. For example, the chromosome *3q* locus has been linked to both psoriasis and RA and associated with psoriasis.[45,120,121] The gene *SLC12A8* (solute carrier family 12, member 8), which maps to this region, was thought to be a strong candidate psoriasis susceptibility gene, but no association was demonstrated.[120] However, the same gene has been associated with PsA in a recent German study, although this finding requires replication in other populations.[122]

Another region of overlap is 1p36, and this region is interesting because it has been linked in both psoriasis and RA families.[38,123] It harbors the tumor necrosis factor receptor II (*TNFR2*) gene, which has been shown to be associated with familial RA in both UK and European populations.[124,125] Recent work showing the response of PsA patients to treatment with soluble recombinant TNFR2 fusion protein lends support for a role for this pathway in PsA pathogenesis, and the gene is therefore a strong candidate PsA susceptibility gene.[87]

Chromosome *17q* is another region that shows overlap in a number of linkage studies of RA and psoriasis. Recently, an association of a region of chromosome *17q25* containing the *SLC9A3R1* (solute carrier family 9, isoform 3 regulatory factor 1) and the *NAT9* (encodes a new member of the N-acetyltransferase superfamily) genes has been reported with psoriasis. A polymorphism lying between the two genes leads to disruption of a binding site for a regulatory molecule, RUNX1. This is thought to lead to defective regulation of one or both genes, resulting in susceptibility to psoriasis.[126] The association of this polymorphism has not yet been investigated in PsA patients.

Using the approach outlined here, it should be possible to identify PsA susceptibility genes which show overlap with either psoriasis or IA. However, without performing a WGS on PsA families, regions that are linked uniquely with PsA will not be identified. Recently, the first WGS using solely PsA families has been reported.[127] These families were collected using the Icelandic genealogical database, and comprised extended pedigrees of up to and including seven meioses. One hundred and seventy-eight PsA patients from 39 families were identified. A susceptibility locus was identified on chromosome *16q* with a logarithm of odds (LOD) score of 2.17. When the analysis was restricted to paternal transmissions only, the LOD score increased to 4.19. The phenomenon of paternal transmission in PsA has also been reported previously.[128] The region of linkage on chromosome *16q* is in close proximity to the *CARD15* gene.[118] Interestingly, chromosome *16q* has also been found

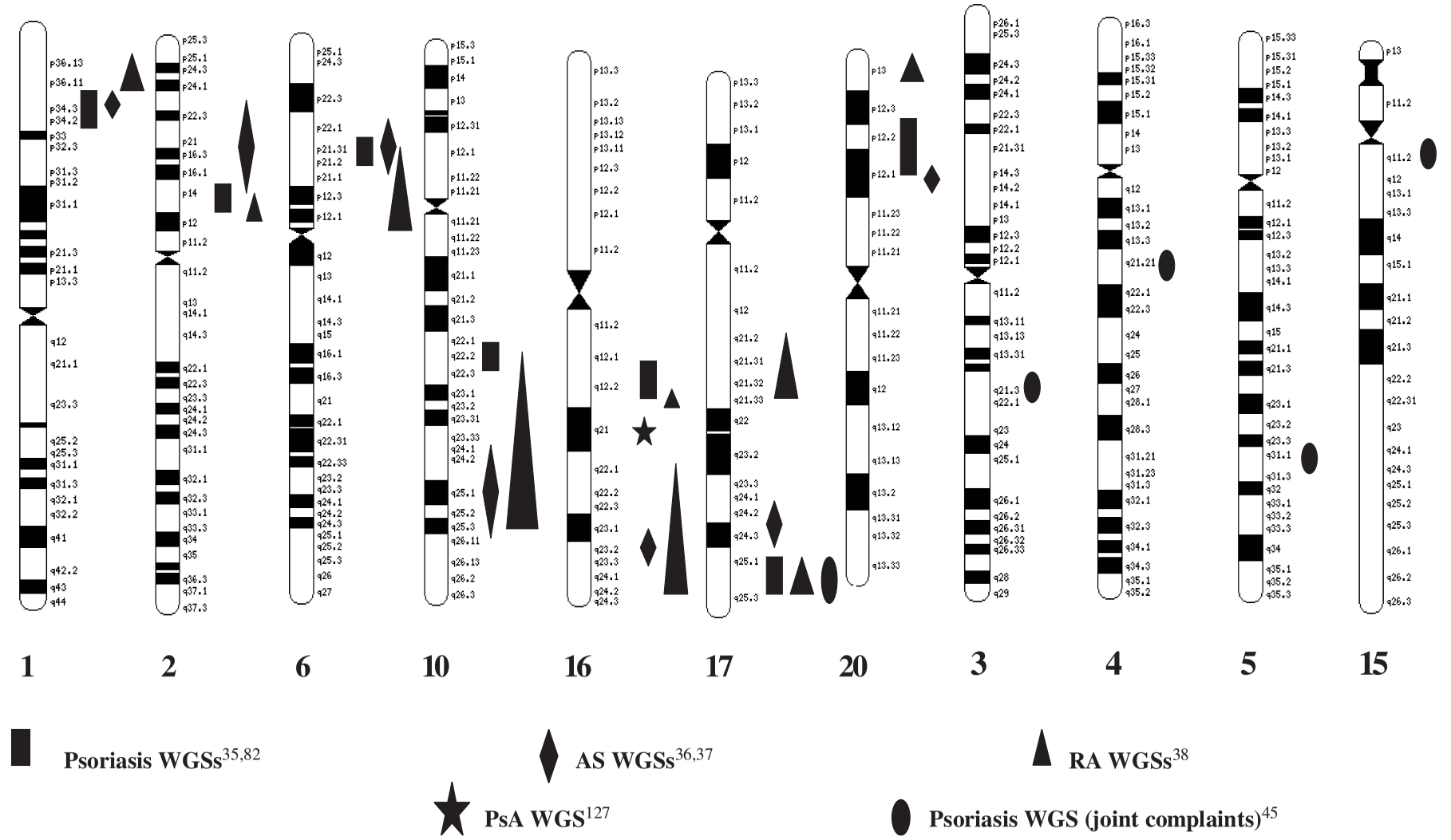

Fig. 1. Regions of overlap from linkage studies of psoriasis, RA, AS, and PsA families

to be linked to psoriasis, RA, and AS.[35–38] Therefore, this region warrants further investigation to determine whether a PsA susceptibility gene resides within it.

Summary and conclusion

Most clinicians agree that PsA exists as a separate entity, but the identification of genetic susceptibility factors would help to confirm that PsA is not simply the co-occurrence of IA and psoriasis. The identification of novel susceptibility factors might also allow the development of novel therapies or better targeting of existing therapies. This is important because PsA was previously thought to be a benign disease, but increasing evidence has suggested that it causes significant morbidity with almost 20% of the patients developing deforming arthritis.[66,129,130] Although a community-based study suggested that PsA has no significant increase in mortality compared with the general population,[14] hospital-based studies have shown an increased risk of death, with a standardized mortality ratio of 1.59 for females and 1.65 for males. Furthermore, patients with a more severe disease have increased mortality.[131,132] PsA patients tend to be treated with medical therapies dictated by those targeted for RA. If RA and PsA are two distinct diseases, the efficacy and safety of treatments for RA would not be expected to equate to those for PsA, and evidence suggests that these treatments are less effective in PsA.[87,133,134]

Both linkage- and association-based approaches have been used in order to identify PsA susceptibility genes. Linkage to 16q has recently been demonstrated in the first WGS of PsA families. A number of candidate genes have also been investigated, but some studies show conflicting results and few have attempted to distinguish PsA genetic susceptibility factors from those contributing to IA or psoriasis. Furthermore, most of the studies examined a small series of patients. Association to both *MICA* and *TNF* have been replicated in independent data sets, and association has recently been reported to genes residing outside the 6p21 region. In addition, a number of regions show linkage in WGS of both psoriasis and either RA or AS. Such regions are strong candidate PsA susceptibility regions. In order to follow up these linkage studies using association-based approaches, large numbers of PsA cases will be required. This will allow stratification analysis to be performed to investigate whether different genes contribute to susceptibility in different subsets of PsA, while still retaining reasonable sample sizes. In addition to comparing patients with PsA with healthy controls, it is important to control for psoriasis and IA. Only by using this experimental design will it be possible to dissect out susceptibility genes that are unique to PsA over and above those that contribute to psoriasis alone and IA alone.

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