GENETIC EPIDEMIOLOGY OF PSORIATIC ARTHRITIS

by

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Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis. The etiology of PsA is multifactorial with compelling epidemiological and immunogenetic evidence to implicate a strong genetic predisposition. Therefore a positional cloning strategy offers a potential approach to elucidate the genetic basis of this complex trait. In this thesis, three studies were designed using a well characterized PsA population, in an attempt to minimize the genetic (locus) heterogeneity of PsA. This will help facilitate the prospects of identifying susceptibility regions for PsA. The first study compared the clinical and immunogenetic factors of sporadic versus familial PsA. We noted a markedly younger age of onset of psoriasis and inflammatory arthritis in the familial group. The second study further characterized the PsA phenotype by comparing the clinical and immunogenetic features of those with early versus late onset psoriasis. Early onset psoriasis in patients with PsA appeared to be a more homogenous subset of PsA exhibiting a stronger association with HLA antigens previously demonstrated to be associated with psoriasis and PsA. In the third study we compared the penetrance and expression of PsA in offspring of affected mother versus an affected father, in order to determine whether a parent of origin effects exists at the phenotypic level in PsA. We demonstrated an excess paternal transmission in PsA. Defining a more homogeneous subset of PsA and postulating a non-Mendelian mode of transmission will likely assist in the fine mapping and ultimate cloning of susceptibility loci for PsA.
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List of Abbreviations

ANA - antinuclear antibody

ARA - American Rheumatism Association

AS - ankylosing spondylitis

ASA - acetyl-salicylic acid

DNA - deoxyribonucleic acid

ESR - erythrocyte sedimentation rate

HIV - Human immunodeficiency virus

HLA - human leukocyte antigen

IBD - identity by descent

IDDM - insulin dependent diabetes

MHC - major histocompatibility complex

NSAIDs - non steroidal anti-inflammatory drug

NIDDM - non insulin dependent diabetes

PASI - psoriasis area severity index

PsA - psoriatic arthritis

PUVA - psoralen ultra-violet A

RA - rheumatoid arthritis

RF - rheumatoid factor

SMR - standardized mortality ratio
Psoriatic arthritis is an inflammatory joint disease associated with psoriasis (1). It is manifested by heterogeneous clinical features associated with relapsing and remitting symptoms. Once considered to be a variant of rheumatoid arthritis, epidemiological studies now suggest that psoriatic arthritis is a distinct clinical entity with its own demographic, clinical and radiographic features (2).

The etiology of psoriatic arthritis is unknown. However, there is compelling evidence to indicate that the susceptibility to psoriatic arthritis is inherited, albeit not in a simple monogenic fashion (3). The evidence for the genetic basis of psoriatic arthritis is gathered from population based family
studies, association studies with HLA antigens and mounting evidence for the strong genetic contribution of psoriasis, a related disorder (3).

With recent advances in molecular biology, semi-automated genotyping and improvements in genetic analysis, geneticists are now able to dissect the genetic basis of complex traits. This is evidenced by insights that have already been made in complex diseases such as diabetes, asthma and Crohn's disease (4). Human linkage analysis offers an attractive strategy for elucidation of the genetic basis of complex disorders. This is particularly relevant for psoriatic arthritis because of the strong heritability of this disorder. At present no susceptibility locus has been identified for psoriatic arthritis as linkage studies have not been attempted in this disorder. A genome wide scan for psoriatic arthritis is currently being planned at the University of Toronto Psoriatic Arthritis Clinic.

A successful genome wide scan will result in the identification of candidate regions where the susceptibility genes are suspected to reside. Although simply mapping the genes to a specific region is not an end in itself, this will greatly facilitate the identification of gene(s) responsible for psoriatic arthritis through subsequent physical mapping. Identification of the gene(s) and their product(s) will undoubtedly have many rewards. The gene(s) will provide insight into the pathogenesis of psoriatic arthritis and thus help direct functional studies aimed at elucidating the precise mechanism of disease. The gene products may lead to new molecular targets that could aide in the design
of more specific anti-psoriatic arthritis drugs. Identification of the gene(s) responsible for psoriatic arthritis may also serve as an important prognostic marker and assist in counseling relatives regarding their risk of being affected.

The success of a linkage study depends on many factors at each of the following steps: i) identification of pedigrees segregating with the disease of interest, ii) ability to limit genetic heterogeneity, iii) typing of DNA markers on available family members to define broadly the location of the disease locus, iv) and further refinement and cloning of the disease gene (5).

One of the most formidable obstacles faced in the analysis of a complex trait is the genetic (locus) heterogeneity inherent to the disorder (5). Genetic heterogeneity refers to mutations in any one of several genes that may result in identical phenotypes. Locus heterogeneity hampers genetic mapping, as a chromosomal region may cosegregate with the disease in some families and not in others.

In this thesis, we will investigate ways to minimize the heterogeneity of psoriatic arthritis, using a well characterized, prospectively followed population of psoriatic arthritis patients. This will done by 1) comparing the characteristics of sporadic versus familial cases of psoriatic arthritis, 2) further characterizing psoriatic arthritis according to the age of onset of psoriasis, 3) and assessing an alternative non-Mendelian mode of transmission in psoriatic arthritis. The findings from these studies should facilitate future linkage studies in psoriatic arthritis through better characterization of a more homogenous phenotype and
refinement of the genetic model in psoriatic arthritis.
Chapter 2 - Background

2.1 The Phenotype

Epidemiology

The original association between psoriasis and arthritis was noted by Albert in 1818 (6). As both psoriasis and arthritis are common conditions, it was initially argued that the co-existence of the two disorders in the same patient did not represent a unique disease entity (7-10). However the reported prevalence of psoriatic arthritis is far greater than one would expect if their co-existence occurred by chance alone (11). Therefore epidemiological studies support the concept of psoriatic arthritis.
Psoriatic arthritis was then considered by some to be a variant of rheumatoid arthritis. However with the discovery of the rheumatoid factor, it was noted that most patients with psoriatic arthritis were seronegative for this autoantibody as compared to rheumatoid arthritis patients that were seropositive for the rheumatoid factor 70% of the time (2). It then became clear that psoriatic arthritis was distinct from rheumatoid arthritis. Presently, psoriatic arthritis is classified among the seronegative spondyloarthropathies. This is because psoriatic arthritis is manifested by peripheral arthritis, spondylitis in 40% of patients, and is usually associated with HLA-B27 antigen, which are all classic features of a seronegative spondyloarthropathy.

Psoriasis is a chronic inflammatory skin disorder that affects approximately 1 to 2% of the North American population (12). Psoriatic arthritis refers to the inflammatory arthritis associated with psoriasis (11). Psoriatic arthritis occurs in about 10 to 40% of the patients afflicted with psoriasis. The wide distribution in frequency of inflammatory arthritis in psoriasis is likely attributable to the lack of validated criteria for psoriatic arthritis, as well as selection bias in earlier studies. Overall, the prevalence of psoriatic arthritis is the same for both males and females. However, there are slight differences among certain subsets of the disease. Males have a slightly higher prevalence of distal arthritis and spinal disease while females exhibit a higher prevalence of polyarthritis (11,13). Psoriatic arthritis usually occurs in the third or fourth decade of life, although this entity has been recognized in children. There is
very little information regarding the racial and ethnic associations of psoriatic arthritis.

Clinical Features

Psoriatic arthritis is a heterogeneous disease with articular and extra-articular manifestations. Based on the articular involvement the disease is classified into five subsets: asymmetric oligoarthritis, symmetric polyarthritis, distal interphalangeal joint arthritis, arthritis mutilans, and spondyloarthropathy (14). The onset of arthritis is usually insidious, but it can occur acutely. Variability in definition of symmetry, peripheral and axial overlap pattern has led to differences in the reported frequency of the subsets of psoriatic arthritis.

Asymmetric oligoarthritis has traditionally been recognized as the most common form of arthritis, accounting for approximately 70% of cases. However, more recent studies suggest that the prevalence of asymmetric oligoarthritis has been over represented. The prevalence of oligoarthritis and polyarthritis appears to be related to the duration of the disease. In studies where the disease duration of psoriatic arthritis patients was less than 5 years, the oligoarticular pattern was reported to be the most common subset. However, more recent studies which have followed patients for over 10 years, note that the polyarticular pattern is the most common (15, 16). The latter studies report a prevalence for polyarthritis to be up to 40% for psoriatic arthritis. It should be noted that a patient is not confined to a particular pattern of arthritis. In fact
more than 60% of patients change from their initial pattern (16). Whether the presenting or subsequent pattern is of prognostic value has not been resolved.

The distal interphalangeal joint is involved in over 50% of psoriatic arthritis patients. However the distal interphalangeal of psoriatic arthritis refers to the sole involvement of the distal interphalangeal joint. Some studies have estimated the prevalence of distal interphalangeal joint variant of psoriatic arthritis to be as high as 12% (17). However, whether this is the sole articular manifestation of psoriatic arthritis has been questioned recently (2).

Spondyloarthropathy develops in 20% to 40% of patients, but is rarely detected at the onset of psoriatic arthritis (16). Spondyloarthropathy usually occurs in conjunction with another pattern of peripheral arthritis, but in a small proportion of patients it can occur in the absence of peripheral joint involvement (less than 5%). Arthritis mutilans, the most destructive and devastating consequence of psoriatic arthritis, occurs in 5 to 10% of patients (16).

A characteristic feature of psoriatic arthritis is dactylitis, which refers to a diffuse swelling of the entire digit along with arthritis of the distal interphalangeal, proximal interphalangeal, and metacarpophalangeal or metatarsophalangeal joints. This occurs in approximately 30% of patients (14,18). Enthesitis, which refers to inflammation at the site of tendon insertion to bone, is also a common manifestation in psoriatic arthritis. The heel is a common site of enthesitis experienced by psoriatic arthritis patients and often results in significant discomfort and disability.
The inflammatory process in psoriatic arthritis can involve sites other than the articular system. With respect to skin changes, the classic form of psoriasis vulgaris is the major type of psoriasis noted in psoriatic arthritis patients. Pustular psoriasis and erythroderma have also been reported in patients with psoriatic arthritis (19). In approximately 70% of cases, psoriasis precedes the onset of arthritis, but the interval between the onset of psoriasis and arthritis can be extremely variable. In fifteen percent of individuals, the skin and joint manifestations occur simultaneously. In the remaining 15% of cases, the joint disease precedes the skin manifestations. Nail lesions, including pits and ridges, as well as onycholysis have been shown to signal the development of psoriatic arthritis (20). These changes occur in 90% of patients with psoriatic arthritis and 41% of patients with uncomplicated psoriasis (psoriasis without arthritis). No consistent relationship has been noted between the severity of skin lesions and the extent of joint inflammation in psoriatic arthritis (20).

Other less frequent, extra-articular features of psoriatic arthritis include ocular involvement (particularly anterior uveitis), aortic insufficiency, mucus membrane lesions and colitis (7,14).
Laboratory studies

There are no specific laboratory investigations that aid in the diagnosis of psoriatic arthritis. The laboratory abnormalities that occur are similar to those of any chronic inflammatory process. Acute phase reactants such as the erythrocyte sedimentation rate (ESR) are elevated in approximately 40 to 60% of patients (19). This is particularly evident in patients with the polyarthritis variant of psoriatic arthritis. Recent studies have shown that 5 to 16% of psoriatic arthritis patients have a low titer of rheumatoid arthritis while 2 to 16% are noted to have a low titer antinuclear antibody (14,18,20). These antibodies do not appear to have any apparent clinical significance as their presence does not correlate with any particular clinical feature.

Radiographic findings

Characteristic radiographic features of psoriatic arthritis include soft tissue swelling, periarticular bone erosions, resorption of the distal phalanx, prominent new bone formation, asymmetric joint involvement, and paravertebral ossification (14). The most characteristic change in the peripheral joint is the "pencil-in-cup" picture of marked lysis of the distal end of a phalanx with remodeling of the proximal end of the more distal phalanx. The presence of spurs and periosteal reaction are characteristic of the enthesopathy of psoriatic arthritis. In the spine, both typical marginal syndesmophytes and paramarginal syndesmophytes are seen.
**Diagnosis**

There are no diagnostic or classification criteria for psoriatic arthritis. A definitive diagnosis of psoriatic arthritis should include the unequivocal presence of psoriasis and inflammatory arthritis both of which have been confirmed by a physician. The diagnosis can occasionally be difficult as psoriasis may present in areas of the skin that are often overlooked in clinical examination such as the gluteal folds, scalp and umbilical region. Secondly the skin and joints are characterized by a remitting and relapsing nature. Thus the skin lesions or joint manifestations may not be present at the time of the clinical assessment by the physician. The diagnosis of psoriatic arthritis is particularly difficult in the absence of psoriasis. In such cases, clinical and radiographic features, including the pattern of the arthritis, the distribution of the joints involved, and the presence of a spondyloarthropathy may facilitate the diagnosis.

**Clinical course and outcome**

The course of psoriatic arthritis can be quite variable ranging from a benign monoarthritis to a deforming destructive polyarthritis. It is also characterized by frequent flares and periods of remission. Joint damage is thought to progress despite control of the inflammatory process of the disease. In assessing the progression of psoriatic arthritis after 5 years of follow up, the
number of patients with five or more damaged joints more than doubled (14,22). Furthermore in a recent cross-sectional study, 57 percent of psoriatic arthritis patients had erosive arthritis and 19 percent had American Rheumatism Association (ARA) class III or IV functional impairment (23). A younger age at the onset of arthritis, female gender, and acute onset of arthritis are more common in patients with deforming arthritis. A recent study noted that seven percent of patients eventually undergo musculoskeletal surgery (24). The average disease duration prior to the first surgery was 13 years. The number of actively inflamed joints and the extent of radiological damage at first assessment were highly predictive for subsequent surgery.

The mortality of psoriatic arthritis patients followed in a single large outpatient clinic has been noted to be higher than the general population (25). The above study followed 441 psoriatic arthritis patients longitudinally of which twelve percent died. The standardized mortality ratio (SMR) for the male and female cohort was 1.65 and 1.59 respectively (25). Thirty-six percent of the deaths were attributed to disease of the circulatory system, 21% due to respiratory system, 17% due to malignant neoplasm, and 15% due to injury or poisonings. A subsequent multivariate analysis revealed that erythrocyte sedimentation rate (ESR) > 15mm/hour, medication use prior to initial visit, radiologic damage and absence of nail lesions were associated with an increased overall mortality (26).
Treatment

The goals of therapy in psoriatic arthritis are to induce remission of the skin lesions, alleviate articular symptoms, and prevent joint destruction. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the initial drugs of choice for the inflammatory arthritis. The efficacy of different NSAIDs are similar when administered in equivalent therapeutic doses. In individuals whose arthritis is persistent, disease modifying drugs can be used. If the skin disease is well controlled with topical medication, the joint disease can be treated with wide range of second line or cytotoxic drugs (22-32). These include sulfasalzine, gold salts, antimalarials and azathioprine. In patients with severe skin inflammation, medications such as methotrexate, retinoic acid derivatives, or psoralen plus ultraviolet light (PUVA) should be considered (33-40). These medications have the added benefit of treating both the skin lesion and joint manifestations. Corticosteroids are usually avoided as their discontinuation may exacerbate psoriasis.

In summary, psoriatic arthritis is a clinically heterogeneous disorder, characterized by numerous articular patterns and extra-articular features. The course of psoriatic arthritis is quite variable.
2.2 Etiology of psoriatic arthritis

The etiology of psoriatic arthritis is likely due to a complex interaction between genetic, immunological and environmental factors (41,42). The evidence for the genetic basis of psoriatic arthritis is based on population studies, consistently strong HLA associations and from genetic studies in psoriasis. A comprehensive review of the genetic epidemiology of psoriatic arthritis is presented in this section. But first a brief overview of the immunological and environmental factors postulated to be involved in the etiology of psoriatic arthritis will be discussed.

Immunological

There is accumulating evidence to support the role of the immune response in initiating and/or perpetuating the inflammatory process in psoriatic arthritis (43). However the precise nature of this mechanism by which an aberration in the immune system can predispose to psoriatic arthritis has not been elucidated. Support for the immune abnormalities in psoriatic arthritis includes the presence of a lymphocytic infiltrate in both skin and joint lesions, the presence of circulating immune complexes in the serum as well as abnormalities in cytokines, growth factors, and adhesion molecules (44-51).

Environmental

Environmental factors have also been implicated in the pathogenesis of psoriatic arthritis. Infection and trauma have long been recognized as potential
triggers of psoriasis and psoriatic arthritis. The temporal relationship between certain viral and bacterial infections in the exacerbation and development of psoriasis and psoriatic arthritis is well established (52,53). In patients with psoriasis, streptococci have been isolated in 26% to 79% of throat cultures with 56% to 85% of patients having serological evidence of a recent streptococcal infection (54). Similar trends have been identified in patients with psoriatic arthritis. An increased prevalence of Chlamydia has also been noted in patients with psoriatic arthritis. Finally, both psoriasis and psoriatic arthritis appear to exhibit a higher prevalence among those individuals infected with HIV (55,56).

In patients with psoriasis, even minor trauma to the skin can result in the development of a psoriatic plaque, the so called Koebner’s phenomenon (57). A retrospective search of medical records revealed that 12 of 138 patients with psoriatic arthritis experienced trauma before the onset of arthritis as compared to only 2 of 138 rheumatoid arthritis patients. However, the clinical and laboratory findings of 25 post-traumatic PsA patients was similar to 275 PsA patients without a history of trauma, except for ESR and CRP at disease onset (58). These differences in acute phase responses were not sustained in the follow-up period. It has been suggested that trauma induced arthritis represents a deep Koebner phenomenon, perhaps related to peripheral nerve release of substance P. Support for this contention is derived from data in recent studies which have noted the occurrence of arthritis and acro-osteolysis following traumatic events (59).
Genetic basis of psoriatic arthritis

Population Studies in Psoriatic Arthritis

The most convincing epidemiological study suggesting familial clustering of psoriatic arthritis was done by Moll and Wright in 1973 (60). The remaining studies assessing the familial tendency of psoriatic arthritis were small, and often with poor phenotype ascertainment. However these studies also noted familial clustering of psoriatic arthritis (60).

Moll and Wright assessed first and second degree relatives of 88 patients with established psoriatic arthritis and 20 subjects with psoriasis and other forms of arthritis. Probands were ascertained from a hospital population in United Kingdom (UK) and sampling was consecutive and unselective. Of the probands with psoriatic arthritis, 12.5% had at least one relative with confirmed psoriatic arthritis. Of the 181 first degree relatives assessed, 10 had psoriatic arthritis, which included 5 siblings. Therefore, 5.5% of the first degree relatives were noted to have psoriatic arthritis. The calculated prevalence of psoriatic arthritis in the UK population was 0.1% \((p < 10^{-8})\). The authors expressed the degree of familial aggregation using the Kellgran factor \((K_p)\), and noted a heritability \((K_p)\) of 48 (61, 62). The relative risk of affected first degree relatives with psoriatic arthritis according to Risch \((\text{prevalence of psoriatic arthritis in first degree relatives of probands with psoriatic arthritis over population prevalence of psoriatic arthritis in the general population} (\lambda_1)\) was 55.
(95% CI 45.8 - 68.7) (63). The recurrence risk for an affected sibling ($\lambda_s$) could not be calculated as the total number of siblings ascertained was not reported. The most conservative estimate for ($\lambda_s$) would be 27, assuming all first degree relatives ascertained were siblings.

The recurrence risk of relatives ($\lambda_R$) is the current method to assess the degree of familial clustering in complex disease. The higher the value of lambda the greater the strength for the genetic contribution. By convention a recurrence risk of greater than 2 suggests a significant genetic contribution for a complex disease (4). The recurrence risk of siblings ($\lambda_s$) for diabetes is 10-15, systemic lupus erythematosus is 15-20 and hypertension is 2-3 (64). Thus based on the magnitude of the recurrence risk among first degree relatives ($\lambda_1$ 55) and siblings ($\lambda_s$ at least 27), psoriatic arthritis appears to exhibit a strong genetic predisposition.

The prevalence of psoriasis in probands with psoriatic arthritis was significantly higher than in population controls. Both the Kellgran factor (Kp) and heritability among first degree relatives as calculated according to Risch ($\lambda_1$) for psoriasis was 19 in the first degree relative of psoriatic arthritis probands. Thus the presence of psoriatic arthritis in the probands increases the likelihood for a family member to develop psoriasis. This implies that there is a common genetic susceptibility for both these disorders.

The clinical features in affected first degree relatives of patients with psoriatic arthritis included 47% with psoriasis and 17% with psoriatic arthritis.
As psoriasis often precedes psoriatic arthritis, it is conceivable that psoriatic relatives without arthritis represent psoriatic arthritis sine arthritis.

**Twin Studies in Psoriatic Arthritis**

There are no reports of twin studies in psoriatic arthritis. However, Moll and Wright reported a triplet born with an identical twin and a non identical third triplet (60). Both identical twins developed psoriasis with one having spondylitis and the other polyarthritis. The non identical twin had no psoriasis or arthritis. Segregation analysis has not been attempted in psoriatic arthritis.

**Association studies in Psoriatic Arthritis**

Most HLA studies in psoriatic arthritis were done by serologic techniques (65-72). The association between HLA antigens and psoriatic arthritis has been used to identify patients destined to develop psoriasis and psoriatic arthritis. HLA antigens -B17, -B16 and its splits -B38 and -B39, as well as -Cw6 are associated with psoriasis and psoriatic arthritis. HLA-B7 and B27 are associated with psoriatic arthritis alone. In addition, HLA antigens may identify patients with a particular pattern of psoriatic arthritis. Examination of HLA antigen distribution among the different clinical patterns of psoriatic arthritis revealed that HLA-B27 is associated with back involvement among patients with psoriatic arthritis, while B38 and B39 occurred more frequently among patients with peripheral polyarthritis (65,67,72). Psoriatic arthritis patients exhibiting a symmetric polyarthritis resembling rheumatoid arthritis, showed a significant increase in HLA-DR4 (72).


**Linkage studies in Psoriatic Arthritis**

Based on the results of the study by Moll and Wright and from numerous association studies which suggest a strong genetic contribution in the etiology of psoriatic arthritis, a linkage study is warranted. To the best of our knowledge there are no reports of any linkage studies in psoriatic arthritis. Our centre is presently ascertaining multicase families with psoriatic arthritis in an attempt to carry out first linkage study in psoriatic arthritis.

**Genetic Basis of Psoriasis**

Psoriatic arthritis and psoriasis are related in that most patients with psoriatic arthritis also have psoriasis. Furthermore, a high prevalence of psoriasis in first degree relatives of probands with psoriatic arthritis has been noted. Finally the two disorders share selected HLA alleles. Thus psoriasis and psoriatic arthritis likely share certain common genetic susceptibilities. As a result the genetic epidemiology of psoriasis is of relevance to the elucidation of the genetic basis of psoriatic arthritis, especially since psoriasis has been investigated more extensively. The evidence for the genetic etiology of psoriasis originates from large population based studies (case series, case-control, cohort and twin studies), as well as association and linkage studies.

**Population Based Studies in Psoriasis**

Two large scale epidemiological studies both revealed a substantially higher incidence of psoriasis in relatives compared with the general population. Hellegren et al. noted the prevalence of psoriasis to be 7.8% among first
degree relatives compared with 1.97% in the general population (73). The relative risk of acquiring psoriasis among first degree relatives by Risch's method ($\lambda_1$) was 3.96. Lomholt et al., reported a life time probability of developing psoriasis to be 23% for parents, 23% for siblings, and 25% for children (74). The relative risk of acquiring psoriasis in siblings according to Risch's method ($\lambda_s$) was 8.21.

Twin Studies in Psoriasis

A Danish Twin Registry reported a concordance rate for psoriasis to be 56% in 32 monozygotic twins (75). Two retrospective studies noted a 62 to 70% concordance rate in monozygotic twins as compared to 21 to 23% in dizygotic twins (76,77). The twin studies suggest a strong genetic component to psoriasis but also implicate environmental factors as the concordance rate for monozygotic twins does not reach 100%.

Segregation Analysis in Psoriasis

Numerous segregation studies have been performed in psoriasis to determine the mode of inheritance. After analyzing many large multiplex kindreds of psoriasis, most studies conclude that a polygenic or a multifactorial pattern is the most likely mode of inheritance (78).

Association Studies in Psoriasis

The HLA associations detected initially were with Class I antigens, encoded by the HLA-A, -B, and -C loci of the major histocompatibility complex (MHC) genomic region of 6p. Class I antigens HLA-B13, HLA-B17, HLA-B39,
HLA-B57, HLA-Cw6, HLA-Cw7 have consistently shown a positive association with psoriasis in population studies (78). The largest and most consistently reported relative risk has been with HLA-Cw6 (relative risk: 22). Class II antigens, encoded by the HLA-D region of the MHC have also been studied in psoriasis with HLA-DR4 and HLA-DR7 demonstrating consistent associations (69,70).

Linkage Studies in Psoriasis

Three main genetic loci on chromosome 17q, 4q and 6p have been reported in genome scans (78). Tomfohrde et al., reported a psoriasis susceptibility locus on the distal arm of chromosome 17 (79). They analyzed 8 multiplex families with psoriasis, which included 65 affected members. The largest kindred with 20 affected family members demonstrated evidence for linkage at the long arm of chromosome 17. Another susceptibility locus on chromosome 4q was identified by Mathews et al. who conducted a genome wide scan in a multiplex family with 20 members of which 12 subjects were affected (80). Parametric analysis assuming a dominant mode of inheritance, indicated that a susceptibility locus for familial psoriasis was located on chromosome 4q (maximum LOD score was 3.03 at D4S1535 with θ=0.08). Nonparametric multipoint analysis also demonstrated significant excess allelic sharing (p<0.0026) at the same locus. However, linkage to 4q has not been reproduced by other investigators.
In the largest genome scan to date in 115 families, including 414 affected members (224 sib pairs), recombinant based tests and allele sharing methods revealed linkage to the HLA region (Zmax 3.52) and suggested linkage to two other novel regions (81). The two new regions were on chromosome 20p (Zmax 2.62) and 16q (Z Max 2.50) (a region which overlaps with a recently identified susceptibility locus for Crohn's disease). Independent confirmation of the psoriasis susceptibility locus on chromosome 6p has been reported by two groups (78). Furthermore, the existence of a psoriasis susceptibility locus, in or near the MHC region of chromosome 6 is strongly supported by a lod score analysis of HLA-B and psoriasis in 97 families from 16 published data sets. The recombination fraction between the psoriasis susceptibility gene and HLA-B is estimated to be at or near 0.00, with a maximum two-point lod score of 23.7 (82). Thus the HLA region is most likely involved in the etiology of psoriasis. With the exception of the HLA region the consistency of other susceptibility regions in psoriasis is low, suggesting that they may be either loci of small effects or psoriasis exhibits a high degree of locus heterogeneity. None of the linkage studies in psoriasis specifically addressed linkage to psoriatic arthritis as these studies did not specifically ascertain patients psoriatic arthritis nor confirm the diagnosis.
2.3 Identification of susceptibility regions / genes in complex diseases

A frequently used approach for identification of genes for a complex disorder is based on a strategy where the disease gene is isolated by its chromosomal location, without any knowledge of the function of the gene. This approach is referred to as positional cloning. There are three basic steps involved in positional cloning. The first is localization of the relevant genes to candidate regions where susceptibility loci are suspected to reside. The next step involves isolation of the candidate genes. The third step involves demonstration of gene mutations within the suspected disease genes, thus proving that the candidate gene is indeed the true susceptibility gene.

The initial step of positional cloning requires collection of families with multiple affected individuals so that a linkage analysis can be performed. Presently the two most commonly used methods for linkage analysis are the traditional method (parametric or recombinant based) and allele sharing method (non parametric) (4,5).

The traditional method of linkage analysis involves constructing a model to explain the inheritance of a disease in pedigrees. The traditional method has been very successful in elucidating the genetic basis of simple Mendelian disorders, where the mode of transmission is known. However application of
this method to determine susceptibility loci for complex traits has been much more difficult.

The cornerstone of the traditional method is the estimation of the recombination fraction, denoted $(\theta)$ for a given pedigree. The recombination fraction is defined by the probability that a gamete is recombinant. The closer two loci are to one another the less likely a crossover event will occur (ie the more likely the loci are linked). Thus the recombination fraction is a function of distance, when certain assumptions (mapping functions) are taken into account.

The ideal setting for this approach involves ascertaining multigenerational families with multiple affected members. All family members are genotyped. Subsequently, various assumptions are made regarding the mode of inheritance of disease, frequency of disease alleles, disease penetrance as well as other parameters. Based on these assumptions and the pedigree structure of the family, a likelihood function for the observed data is constructed, which is a function of the recombination fraction. Using this likelihood function, a test of the hypothesis of no linkage between a marker and disease can be performed. This is based on the likelihood ratio statistic:

$$H_0: \theta = 0.5 \text{ (no linkage)} \quad H_a: \theta < 0.5$$

Then "Z" is equivalent to $Z = \log \left( \frac{L(\theta)}{L(\theta = 0.5)} \right)$ where $L(\theta)$ is the likelihood function. The null hypothesis of no linkage is rejected if the value of Z maximized over $\theta$ (0, 0.5) is greater than 3.0.
Numerous problems are encountered during the analysis of complex traits using the traditional method as a multitude of assumptions regarding the model need to be made (5). The following specifications need to be estimated for the traditional method: disease gene frequency, mode of transmission, penetrance of disease genes, phenocopy rate, and marker allele frequency. The estimation of the recombination fraction is also sensitive to pedigree structure, certainty of the diagnosis and the genetic marker information. Inaccurate assumptions can greatly reduce the power to detect linkage. As a result the traditional approach is often not the preferred method for analyzing linkage studies in complex diseases. However, this method is still utilized as useful information can occasionally be delineated under the proper assumptions.

An alternative approach to linkage studies for complex traits is the allele sharing or non parametric method (83). This refers to a set of methods which are based on the following premise: in the presence of linkage between a marker and disease, sets of relatives who share the same disease status will be more alike at the marker locus than one would expect if the two loci were segregating independently. The similarity at the marker locus is measured by counting the number of alleles shared identical by descent (IBD) in two relatives. Alleles are considered IBD if they are descendants of the same ancestral lines. For example, the expected frequency of IBD sharing of two alleles for mating of heterozygous parents is 25%, 50% and 25% for 0, 1 and
alleles. The closer the marker locus is to the disease locus, the more likely these proportions will be skewed. Linkage is stated to occur if there is a significant distortion of these proportions. In the allele sharing method penetrance is not a confounder as it only includes siblings that share the same disease status. However, this method may lack power as compared to the traditional method. In order to overcome this limitation a larger number of multicafe families are required in the allele sharing method as compared to the traditional method.

Difficulties encountered in the genetic analysis of complex traits using linkage studies include: incomplete penetrance (phenotype is variably expressed despite having the genotype); phenocopies (disease phenotype results from causes other than the gene being mapped); genetic (locus) heterogeneity (when two or more loci can independently cause disease); epistasis (interacting genotypes at two or more unlinked loci); gene environment interactions (where environmental factors can also contribute to disease susceptibility) and insufficient recruitment of family members.

The ability to successfully identify a susceptibility region using the positional cloning approach in part depends on how well one is able to overcome these limitations. Phenocopies can be reduced by strict adherence to diagnostic criteria with minimal inclusion of patients with atypical features. Incomplete penetrance can be overcome by using the allele sharing method as all relatives analyzed in this method express the phenotype. Sufficient number
of families are ascertained through extensive collaborations and well publicized recruitment campaign, as evidenced in recent genome scans in diabetes and rheumatoid arthritis (5). Epistasis and gene environment interactions are daunting tasks to overcome prior to the identification of the susceptibility genes. The next section will address ways to overcome or at least minimize genetic (locus) heterogeneity in psoriatic arthritis.
Chapter 3  Rationale / Hypothesis

3.1 Methods to minimize genetic heterogeneity

Complex diseases are usually manifested by a wide spectrum of clinical features. Psoriatic arthritis is no exception. This disorder is quite heterogeneous as demonstrated clinically by its variable age at onset, clinical features, and radiological manifestations. Thus genetic (locus) heterogeneity is likely to be high in psoriatic arthritis. This is a serious obstacle to overcome in linkage studies as the phenotype can be caused by mutations at any one of several loci (5). In such cases, evidence for linkage to a locus in one family may be offset by evidence against linkage in another family. Even a modest degree of heterogeneity may significantly weaken the evidence for genetic linkage (5).
The potential solutions to limit the heterogeneity involves the following global strategies: transform the complex disease into a more homogenous subset or explore novel mechanisms of disease transmission that may account for the non-Mendelian inheritance of the complex trait.

With respect to transforming a complex trait into one or more homogenous phenotypes, this can be done by splitting the disorder based on the phenotype, studying a single large pedigree, focusing on one ethnic group, or by limiting the study to a single geographic region. Further characterization of a phenotype usually has the effect of increasing the recurrence risk for relatives ($\lambda_R$) and may also reduce the number of contributing loci (4,5). These measures may also enhance the identification of a subset of families that show a Mendelian pattern of disease transmission, allowing more powerful model-based methods to be used in the linkage analysis.

Splitting the phenotype may be the best and most direct way to limit the genetic heterogeneity. The goal here is to discover a clinical phenotype which accurately distinguishes between the different genetic forms. Therefore the clinical disorder is transformed from a heterogeneous condition into two or more homogenous disorders. Unfortunately, there is no uniformly accepted method for correctly splitting a disease into the various genetic forms. It would be ideal to split the disorder into subgroups based on biological factors known to differentiate the disorder into more homogenous groups. These subgroups can then be analyzed separately in a linkage study. Approaches in splitting the
phenotype that have successfully led to the reduction in the genetic variability, and subsequent identification of a gene include stratification based on:

1) Clinical phenotype: The successful cloning of the APC gene on chromosome 5 for colon cancer was found when the phenotype was restricted to extreme polyposis (84). In this case an apparent complex trait was narrowed to a simple autosomal one.

2) Age at onset: Maturity onset diabetes of the young (MODY) is a subset of non insulin dependent diabetes (NIDDM) that shows an earlier age of onset (5). Segregation analysis from families of this disorder revealed an autosomal dominant transmission pattern. Subsequent studies revealed that a mutation in the glucokinase gene accounts for 50% of cases of MODY. It is hoped that the gene discovered for MODY will help elucidate disease pathways for the more common non insulin dependent diabetes (NIDDM) and insulin dependent diabetes (IDDM). Susceptibility genes for breast cancer and Alzheimer’s have also been identified by stratifying patients according to the age of onset of the clinical disorder (5).

3) Family history: A condition with a “high genetic load” can be selected by studying families that have multiple affected members. Such was the case with hereditary nonpolyposis colon cancer, which was mapped by defining the trait to require the presence of at least two other affected relatives (4,5).
4) Severity: Focusing on extreme ends of a trait, whether it be mild or severe, can occasionally be very helpful. This is especially true for a continuous trait (4).

Recently, certain novel genetic mechanisms have been proposed which could explain some aspects of non-Mendelian inheritance in complex disorders. These include triplet expansion mutations (anticipation), genomic imprinting, and mitochondrial-related inheritance (85). Anticipation is the primary characteristic of a dynamic trinucleotide repeat sequence mutation and is defined as the occurrence of an inherited trait that progressively increases in severity in successive generations. Measures of severity include recurrence risk, symptoms or age of onset (85). Myotonic dystrophy has been the classical example of a trait which shows anticipation (86). For this autosomal dominant disorder, an increase in the severity of symptoms and a decrease in the age of onset is observed over generations.

Genomic imprinting refers to an epigenetic effect that causes differential expression of a gene depending on the sex of the transmitting parent (87). The imprinting process dictates the expression of a gene from only one parent of a certain sex rather than both genes of a homologous pair. Imprinting is a normal development process that regulates gene expression and is thought to affect a limited number of genes. The first human disorder recognized to be a consequence of genomic imprinting is the Prader-Willi syndrome (87).
Mitochondria contain their own genome. Mitochondrial DNA controls a number of protein components of the respiratory chain and oxidative phosphorylation system, as well as some special types of RNA. A pattern of matrilineal transmission of a disorder is suggestive of mitochondrial inheritance, but is not conclusive. The strongest evidence for a mitochondrial DNA mutation in a genetic disease is in Leber's optic atrophy, characterized by late onset bilateral loss of central vision and by cardiac dysrhythmias (88).
3.2 Hypothesis

The genetic dissection of psoriatic arthritis is still a daunting task due to the low penetrance of susceptibility alleles, influence of the environment and a high degree of genetic (locus) heterogeneity. Attempts to reduce this degree of genetic heterogeneity may be quite helpful in the identification and fine mapping of psoriatic arthritis. In this thesis we attempt to minimize the inherent genetic heterogeneity in psoriatic arthritis by defining a more homogenous subset of psoriatic arthritis and postulating a novel mode of non-Mendelian inheritance by hypothesizing that:

- distinguishing features exist between familial and sporadic psoriatic arthritis (hypothesis 1)
- a more homogenous subset of psoriatic arthritis can be attained by stratifying psoriatic arthritis according to the age of onset psoriasis (hypothesis 2)
- differential transmission of psoriatic arthritis exists at the phenotypic level depending upon the gender of the affected parent (parent of origin effect) (hypothesis 3).

These hypotheses will be tested by:

- comparing the clinical and immunogenetic features of familial versus sporadic psoriatic arthritis (part I).
- further characterizing the clinical and immunogenetic features of psoriatic arthritis according to the age of onset of psoriasis (part II).
- Assessing the differential penetrance and expression of psoriatic arthritis depending upon the gender of the affected parent (part III).
Chapter 4
Clinical Studies

4.1 Study Population

The University of Toronto Psoriatic Arthritis Clinic was established in 1978, as part of an ongoing prospective study. All patients enrolled in this clinic have a confirmed diagnosis of psoriatic arthritis. The diagnosis is based on the presence of an inflammatory arthropathy in association with psoriasis both of which have been verified by a physician at some point in their course. Patients are registered in the clinic if they have psoriatic arthritis and other diseases such as nodular rheumatoid arthritis, systemic lupus erythematosus, gout, inflammatory bowel disease and osteoarthritis are excluded (19). Rheumatoid factor alone is not an exclusion criteria because we have demonstrated that
13% of patients with psoriasis uncomplicated by arthritis have a positive rheumatoid factor (20). Patients are reviewed at initial clinic entry and at 6 to 12 month intervals using a standardized protocol. Each assessment includes a detailed history comprising of questions regarding their skin and joint manifestations, medication history, and extra-articular features. Each patient is specifically asked regarding a family history of psoriasis and psoriatic arthritis in first degree relatives at each visit. A standardized physical examination is performed which includes examination of all major organ systems as well as a detailed peripheral joint and spinal examination. At each visit, the degree of active inflammation and damage in the joints is quantitated and carefully recorded. Plain radiographs of the hands, feet, pelvis, and entire spine are conducted at initial assessment and at 2-year intervals. Although the University of Toronto Psoriatic Arthritis Clinic is considered to be a subspecialty clinic, this clinic encompasses a full spectrum of disease. This is due to our wide referral base which includes primary, secondary, and tertiary referrals. The demographics of our clinic are similar to other clinics in the literature, with respect to disease severity (12).

The number of actively inflamed joints is based on the total number of joints that exhibit stress pain, joint line tenderness or effusions. A damaged joint is defined by the following criteria: persistent restriction of range of movement of > 20% of the range, joint ankylosis or flail joint. The assessment of these
clinical measures has been previously validated and shown to be quite reliable (21).

A treatment scale used to categorize each visit is based on severity of medications used. Treatment either prior to or at each assessment is classified into 6 groups as follows: 0 = no medications, 1 = nonsteroidal anti-inflammatory drugs only, 2 = gold or chloroquine, 3 = methotrexate or azathioprine and 4 = retinoic acid derivative or Psoralen with ultraviolet A, and 5 = oral corticosteroids. The highest level of medication that is attained by the patient is what is recorded for that visit.

The functional class used in this clinic is based on a well accepted and validated global functional status classification scheme (89). In this classification system class I represents normal activities with no pain or discomfort, class II reflects the ability to carry on despite pain or discomfort, in class III activities are limited to those of self care only, and class IV represents those individuals that are confined to bed.

Modified Steinbrocker’s radiographic scoring method, which has been validated for psoriatic arthritis, is used in our clinic to monitor the radiographic progression (90). Using this method each peripheral joint is assigned a score for 0 to IV: 0 being normal, I representing soft tissue swelling, or osteopenia, II showing erosions, III representing erosions and joint space narrowing and IV demonstrating joint space destruction either lysis or ankylosis. The radiological score is recorded as the total number of joints at each stage. Radiological
damage was further defined as mild if only stages I-II were present and severe if stages III-IV were present.

Finally, a routine panel of laboratory tests is performed at each visit including hematological, renal and liver surveillance. Most patients (approximately 70%) that are registered in our clinic have been typed for HLA antigens. Serological methods were initially used for HLA typing, however in the past few years molecular typing for class I and class II antigens has been implemented.
4.2 Part I: Comparison of familial and sporadic psoriatic arthritis

Background
As noted in the background, psoriatic arthritis is a complex disease with heterogeneous features, that exhibits a strong genetic predisposition. Further elucidation of its genetic basis will be enhanced by using a positional cloning approach to identify the relevant genes in psoriatic arthritis. This approach entails ascertaining psoriatic arthritis families with multiple affected members (familial psoriatic arthritis) to test the segregation of a highly polymorphic markers. However, the majority of patients with psoriatic arthritis do not have an affected first degree relative (sporadic psoriatic arthritis) (60).

A comparison of clinical features between familial and sporadic psoriatic arthritis will not only provide a better assessment of the generalizability of the results arising from a linkage study, but any differences identified can be exploited to define a more homogenous subset of psoriatic arthritis patients. This is because familial patients are likely to have a higher "genetic load". Thus clinical features which aggregate within familial groups may help defining a phenotype which is expressed due a particular set of mutation(s). It may also assist in ascertaining multicase families, by identifying a set of distinguishing
features in probands with familial psoriatic arthritis. Therefore it is prudent to be aware of any differences between familial and sporadic psoriatic arthritis.

Differential features between sporadic and familial cases have been noted in selected autoimmune rheumatologic disorders that are somewhat similar phenotypically. In ankylosing spondylitis (AS), 160 patients with familial AS were compared to 160 age and sex matched controls who had no first-degree relative with the disease (sporadic) (91). Familial AS was associated with significantly milder symptoms than sporadic cases as assessed by the spinal mobility score, as well as validated measures of physical activity, social function and pain. However in rheumatoid arthritis, the three major studies that compared clinical, immunological and immunogenetic factors between the familial and sporadic groups detected no significant differences (92-94).

At present, it is unclear how probands with familial and sporadic psoriatic arthritis differ as comparisons between these groups have yet to be performed. We hypothesized that differences exist among clinical and immunogenetic features in familial versus sporadic psoriatic arthritis. Therefore, the objective of our study was to compare probands with familial versus sporadic psoriatic arthritis with respect to clinical, radiological and immunogenetic features at presentation to clinic.
Patient selection and methods

Definitions

Proband

A proband refers to an individual affected with psoriatic arthritis who is enrolled at the University of Toronto Psoriatic Arthritis Clinic. All probands satisfy the accepted definition of psoriatic arthritis (an unequivocal evidence of past or present psoriatic skin lesion and inflammatory arthritis which has been confirmed by a physician).

Multicase families

A multicase family was defined as a family with at least two affected first degree relatives (the proband and at least one additional relative) with either uncomplicated psoriasis or psoriatic arthritis. The multicase families were further subdivided into two mutually exclusively groups: 1) Familial psoriatic arthritis - family with at least one first degree relative with psoriatic arthritis in addition to the proband and 2) Familial psoriasis - family with at least one first degree relative with psoriasis in the absence of psoriatic arthritis in a first degree relative, in addition to the proband. Probands with no family history of psoriasis, psoriatic arthritis or "arthritis" comprised the sporadic group.

Patient selection and methods

All patients registered in the University of Toronto psoriatic arthritis clinic between 1978 and 1997 were enrolled in the study. As part of the standardized clinic protocol each proband was asked specifically regarding a family history of psoriasis or psoriatic arthritis in first degree relatives at each visit. The charts
were reviewed for verification of the presence of a family history of psoriasis and psoriatic arthritis in first degree relatives of our probands. We excluded all patients that reported a family history of “arthritis” in the absence of psoriasis or psoriatic arthritis. The remaining psoriatic arthritis probands were divided into three mutually exclusive groups (defined above): Group 1 - familial psoriatic arthritis; Group 2 - familial psoriasis, and Group 3 - sporadic psoriatic arthritis.

The variables retrieved for each proband at the presentation to clinic are listed in Tables 1 and 2 and can be broadly categorized into the following: demographic information, age of onset variables, disease activity measures, disease damage (as assessed clinically and radiologically), laboratory variables, functional class and HLA antigens. All the variables listed have been prospectively collected in our psoriatic arthritis clinic.

**Analysis**

All statistical tests were performed using the SAS statistical software. We decided a priori that if there were no significant differences in any of the variables at the 10% significant level between familial psoriatic arthritis and familial psoriasis (groups 1 and 2), we would combine these groups and repeat the analysis comparing the combined familial group with the sporadic group. Therefore probands with a family history of a first degree relative with psoriatic arthritis (group 1) were compared to probands with a family history of a first degree relative with psoriasis. Continuous variables were compared using
student t-test, while categorical variables were assessed using a contingency table with chi squared tests. For categorical variables with expected frequencies in any cell less than 5, the Fisher's exact test was used.

**Results**

In total, 407 patients were included. Thirty-six patients (8.8%) were eliminated as they reported a family history of arthritis in the absence of psoriasis. Of the remaining 371 patients, 150 patients (36.9%) reported a positive family history: 52 families (12.8%) with psoriatic arthritis and 98 families (24.1%) with uncomplicated psoriasis. Two-hundred and twenty-one patients (54.3%) had no family history of either psoriatic arthritis, psoriasis, or "arthritis".

Univariate analysis revealed no significant differences between familial psoriatic arthritis (group 1) and familial psoriasis (group 2), as none of the variables reached the 10% level of significance. Therefore groups 1 and 2 were combined and compared against the sporadic group (group 3).

The univariate analysis comparing the clinical and radiographic features of familial (groups 1 and 2) and sporadic group (group 3) revealed several variables to be significant at the 5% level (Tables 1 and 2). Probands in the familial group were younger at presentation to the psoriatic arthritis clinic ($p = 0.003$) and had an earlier age of onset of psoriasis ($p = 0.001$) and inflammatory arthritis ($p = 0.001$). Patients with a family history for either psoriatic arthritis or psoriasis were more likely to have received treatment prior
to presentation to clinic than patients in the sporadic group (p= 0.001) and had a lower number of actively inflamed joints than the sporadic group (p= 0.035). With respect to extra-articular features, probands with a family history of psoriatic arthritis were more likely to have diarrhea (p = 0.008). Rheumatoid factor was found to be more prevalent in the sporadic group (p= 0.041).

Several variables demonstrated significance at the 10% level between the familial and sporadic group. Probands with sporadic psoriatic arthritis were more likely to have greater than 5 clinically damaged joints (p= 0.079), 5 radiographically damaged joints (p= 0.057) and a higher frequency of positive ANA (p=0.072) than patients with familial disease.

With respect to HLA antigens, 292/371 (79%) patients were HLA typed. This included 119 probands in familial group and 173 in the sporadic group (Table 2). HLA-Cw6 was found to be more frequent among patients with familial psoriatic arthritis than sporadic probands (p= 0.083). No other differences were noted in the frequencies of other HLA antigens known to be associated with psoriasis and psoriatic arthritis (HLA - B7, HLA - B27, HLA - B39, HLA - DR4, HLA - DR7 and HLA - DQ3).

Discussion

Epidemiological and immunogenetic evidence suggests that psoriasis and psoriatic arthritis likely share certain genetic susceptibilities (60). This contention is further supported by our results as there were no marked differences in clinical expression in probands with a family history of psoriatic
arthritis as compared to those with familial psoriasis. Therefore in attempting to
determine the genetic basis of psoriatic arthritis, noting the segregation of
psoriasis along with psoriatic arthritis may be quite informative. However it is
conceivable that the absence of any significant difference in any of variables
between familial psoriasis and familial psoriatic arthritis may be due to an
insufficient sample size.

The most striking difference between familial and sporadic probands
was the age of onset of psoriasis and inflammatory arthritis. Probands with
familial disease were significantly younger at presentation of psoriasis and
inflammatory arthritis than probands without a family history (5.6 years for
psoriasis, p < 0.001 and 5.1 years for psoriatic arthritis, p < 0.001). An earlier
age of onset for familial disease has been noted in various other complex
traits (4). Furthermore, splitting a heterogenous phenotype based on the age of
onset has been particularly helpful in the identification of susceptibility genes in
certain complex disorders (4,5). This approach will be discussed more
thoroughly in the next section.

Patients with familial psoriatic arthritis were more likely to be on
treatment for psoriatic arthritis, and were less likely to have active synovitis at
their initial presentation to clinic. In addition, there was a trend for familial
cases to exhibit less clinical and radiological damage at presentation to clinic.
There are two possible explanations for these differences. Given a history of
an affected relative, the proband may be more aware of his/her condition and
therefore seek earlier intervention. An earlier intervention could help alleviate their symptoms and thus lead to less active inflammation and joint destruction. The other possibility is that probands with sporadic psoriatic arthritis have a more aggressive disease with a greater tendency for destructive arthropathy. The present study cannot differentiate between the two, however it is conceivable that both these possibilities may in part be correct as the hypotheses are not mutually exclusive.

The association with diarrhea and familial psoriatic arthritis is intriguing especially since we excluded patients that were diagnosed with overt inflammatory bowel disease from entry into our clinic. A recent linkage study has identified a susceptibility locus on chromosome 16q near marker D16S310 for psoriasis (81). Of interest, a locus conferring susceptibility to Crohn's disease, which is an autoimmune disorder manifested by bouts of diarrhea, has recently been mapped to interval between D16S409 and D16S419 (95). This interval has substantial overlap with the psoriasis candidate region. Furthermore five independent case-control studies have found the prevalence of psoriasis to be markedly increased in patients with Crohn's disease (81). Therefore gene(s) within this region of chromosome 16q may be involved in the pathogenesis of psoriasis and Crohn's disease.

The autoimmune nature of psoriasis and psoriatic arthritis has prompted numerous studies investigating the association between the MHC complex on chromosome 6p and psoriasis as well as psoriatic arthritis. The most
consistently reported association between an MHC antigen and psoriasis is HLA-Cw6 (92). In patients with Type I or familial psoriasis, 78% were noted to be positive for HLA-Cw6 as compared to 20% of patients with late onset or sporadic psoriatic arthritis (96). The significance of this association is not clear as the HLA-Cw6 allele per se may predispose to psoriasis or more likely this allele may be in linkage disequilibrium with a susceptibility allele. In psoriatic arthritis, this association is not as strong. A recent study in psoriatic arthritis has noted that there is a stronger association with other markers on the short arm of chromosome 6 including TNF-alpha and D6S273 than with HLA-C (78). In this study, we noted that the HLA-Cw6 antigen to be associated with familial psoriatic arthritis at the 10% significance level.

Our study has a few limitations. The reliance of the proband's self-reported history for the presence of psoriasis or psoriatic arthritis in first degree relatives, may introduce a potential source of bias. It is likely that some individuals classified as having sporadic psoriatic arthritis have a first degree relative with unrecognized disease. Ideally, the clinical diagnosis of all relatives of the proband included in the linkage study should be confirmed by a physician. However this would have been logistically prohibitive.

To help assess the extent of misclassification we set out to determine the accuracy of the proband's self-reported family history in a subset of our patients. The proband's self-reported family history was compared against the physician's diagnosis in 40 consecutive families with 109 first degree relatives.
This included 70 siblings, 27 parents, and 12 children of the proband. The probands correctly identified 25/32 or 78.0% [95% CI 0.70, 0.86] of family members with psoriasis, 6/12 or 50.0% [95% CI 0.41, 0.59] with psoriatic arthritis and 63/65 or 96.9% [95% CI 0.94, 1.0] that were unaffected (Table 3). The positive predictive values of the proband’s reported history were 25/31 or 80.6% [95% CI 0.73, 0.84] for psoriasis, and 6/7 or 85.7% [95% CI 0.79, 0.92] for psoriatic arthritis (Table 3). The negative predictive value of the proband’s reported history for those individuals that were unaffected was 63/71 or 88.7% [95% CI 0.83, 0.95]. The overall accuracy for our psoriatic arthritis probands to discriminate between psoriatic arthritis, uncomplicated psoriasis and unaffected individuals was 86.2% [95% CI 0.80, 0.92]. The ability to discriminate between affected status (history of either psoriasis or psoriatic arthritis) versus unaffected status was 91% [95% CI 0.86, 0.96]. The probands appeared to be slightly more accurate in determining the correct phenotype of their children (92%) than their parents (85%) or siblings (85%). Ten of the 40 individuals accounted for all 15 misspecifications. Five of the nineteen male probands made at least one error as compared to 5/21 females. Of the 8 relatives that were misspecified as being unaffected by the probands, 2 relatives were not aware of the their affected status (new diagnosis). In the remaining six cases the misspecification was a result of the proband not being fully aware of relative’s affected status.
Therefore from our accuracy study we noted that the proband's history is quite helpful in potentially identifying families with familial psoriasis or psoriatic arthritis as compared to unaffected individuals. The frequency of misclassification of the affected status was 9%. The effect of such misclassification would be to minimize any potential difference between familial and sporadic psoriatic arthritis. Furthermore 14% of the time (5/36 relatives) the proband was not able to distinguish between psoriasis and psoriatic arthritis. Therefore prior to inclusion of any relatives in a linkage study, all relatives must be examined by a physician as misspecification of the phenotype may greatly hamper the prospect of detecting a significant linkage.

The risk of familial disease may simply be a function of the size of sibships, with larger sibships having a greater chance of reporting a positive family history. This is likely not a contributing factor in our study as the number of first degree relatives between the familial (6.85 ± 2.5) and sporadic (6.90 ± 3.2) cases were similar.

Patients with mild sporadic psoriatic arthritis may be less likely to seek a diagnosis than a patient with a family history of psoriasis or psoriatic arthritis given the same level of symptoms, since the latter would have greater awareness of the disease. The effect of disease existence of a family member with the same disease is unclear, but it may result in an improved clinical status for the newly diagnosed family member. For example the index case may
influence the second subject by way of the education and exercise, two factors that may help ameliorate the disease.

Theoretically it is conceivable that the effect of natural selection may have caused the familial disease to have become milder, the notion here being that individuals with very severe disease may be less likely to survive and procreate. Therefore, families that did survive would tend to have more susceptibility genes but fewer severity genes. Although the mortality of psoriatic arthritis is slightly higher than the general population (25), there is no substantial evidence to suggest that such a survival advantage exists.

The probands who reported a family history of "arthritis" in the absence of psoriasis or psoriatic arthritis were not assessed. It has been our experience, that there is a high frequency of misclassification regarding first degree relatives with inflammatory arthritis, based on the probands reporting for "arthritis". This stems from the fact that a large percentage of these relatives with "arthritis" have osteoarthritis rather than an inflammatory arthropathy. We acknowledge that by not including patients with a history of "arthritis" alone, we may have eliminated a small subset of psoriatic patients in whom an inflammatory arthritis presents prior to psoriasis. However we decided a priori, that inclusion of probands with a family history of arthritis would likely weaken any difference between familial and psoriatic arthritis, as a large proportion of these patients will not have an inflammatory arthritis. This raises the broader question of what to do with individuals identified in complex diseases that
demonstrate certain traits for the condition, however do not meet the diagnostic criteria for the disorder. The diagnostic criteria of most rheumatic disorders are designed to improve the simplicity and clarity of the presence or absence of disease. However using these definitions in linkage studies could lead to classifying family members who possess biologically similar but less dramatic pathology as being unaffected. Therefore based on this study we recommend that all relatives need to be carefully assessed for linkage studies, not only for ascertainment of disease status, but also for identification of any traits of a particular disorder, prior to labeling an individual as “unaffected”. Patients with selected features of psoriatic arthritis but failing to meet the accepted definition may need to be stratified prior to the analysis.

The information gathered from our study can also be used to develop a predictive model to identify multiplex families in psoriatic arthritis. Such a model may complement the patient’s self reporting for the presence of multicase family be helpful if the proband is unaware of the affection status of his/her relatives. Based on the results of our study such a predictive model was developed for our clinic (98). Statistically significant variables at the 10% significance level noted in Tables 1 and 2 were reanalyzed using multiple logistic regression. A model was then fitted to determine the probability of having a positive family history. The multiple logistic regression based on univariate analysis revealed 5 variables to be significant. When this model is applied to a patient with onset of arthritis at age 35 (clinic mean), the estimated
probability of a positive family history was 90.1% for patients fulfilling all four variables (presence of HLA-Cw6, diarrhea, medications, radiographic score) and 19.9% for patients not having any variable.

As this was an exploratory study, no attempts were made to correct for the multiple comparisons. Furthermore, the study may have lacked enough power to detect a difference, especially with respect to the frequency of HLA antigens due to the infrequent occurrence of some of the alleles. Therefore our findings need to be interpreted with some caution until replicated by independent groups.

In conclusion, by comparing probands with familial versus sporadic psoriatic arthritis differences in clinical, radiographic and immunogenetic features were noted. The most marked difference noted was the age of onset of psoriasis and inflammatory arthritis in the probands. Probands with familial psoriatic arthritis presented earlier with psoriasis and inflammatory arthritis.
Table 1: Comparison of clinical features between familial and sporadic psoriatic arthritis

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Sporadic PsA N = 221</th>
<th>Familial PsA N = 150</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>gender : % male</td>
<td>56</td>
<td>56</td>
<td>1.000</td>
</tr>
<tr>
<td>age (yrs) at presentation; (mean, sd)</td>
<td>44.7 (13.2)</td>
<td>40.0 (13.7)</td>
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<td>race: % Caucasian</td>
<td>93</td>
<td>100</td>
<td>0.469</td>
</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age at onset of arthritis (mean, sd)</td>
<td>37.4 (12.9)</td>
<td>32.3 (12.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>age at onset of psoriasis (mean, sd)</td>
<td>25.5 (12.9)</td>
<td>31.1 (12.5)</td>
<td>0.001</td>
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<tr>
<td>disease duration: psoriasis (mean, sd)</td>
<td>14.3 (12.4)</td>
<td>15.2 (11.5)</td>
<td>0.552</td>
</tr>
<tr>
<td>disease duration: arthritis (mean, sd)</td>
<td>7.3 (7.7)</td>
<td>7.7 (8.4)</td>
<td>0.680</td>
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<tr>
<td>skin lesion prior to arthritis (%)</td>
<td>72.3</td>
<td>79.0</td>
<td>0.217</td>
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<tr>
<td>nail changes (%)</td>
<td>79.6</td>
<td>84</td>
<td>0.362</td>
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<td>Arthritis pattern at onset (%)</td>
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<td>16.8</td>
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<td>26.9</td>
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</tr>
<tr>
<td>back only</td>
<td>4.6</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>back + distal</td>
<td>0</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>back + oligoarthritis</td>
<td>3.5</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>back + polyarthritis</td>
<td>12.7</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Disease activity / damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of active joints (mean, sd)</td>
<td>10.8 (9.3)</td>
<td>8.6 (7.9)</td>
<td>0.035</td>
</tr>
<tr>
<td># of effusions (mean, sd)</td>
<td>2.5 (3.0)</td>
<td>2.7 (2.7)</td>
<td>0.307</td>
</tr>
<tr>
<td>% &gt;5 clinically damaged joints</td>
<td>20.2</td>
<td>11.8</td>
<td>0.079</td>
</tr>
<tr>
<td>% &gt;5 radiographic damaged joints</td>
<td>37.0</td>
<td>26.8</td>
<td>0.057</td>
</tr>
<tr>
<td>Extra-articular features (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tendinitis</td>
<td>19.4</td>
<td>39.3</td>
<td>0.139</td>
</tr>
<tr>
<td>mucus membrane lesions</td>
<td>25.8</td>
<td>14.8</td>
<td>0.348</td>
</tr>
<tr>
<td>urosethritis</td>
<td>9.7</td>
<td>10.7</td>
<td>1.000</td>
</tr>
<tr>
<td>iritis/conjunctivitis</td>
<td>5.2</td>
<td>4.2</td>
<td>0.786</td>
</tr>
<tr>
<td>malaise</td>
<td>14.6</td>
<td>17.9</td>
<td>0.513</td>
</tr>
<tr>
<td>diarrhea</td>
<td>1.7</td>
<td>8.4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* reflects overall p-value for the entire group using chi-square test
Table 1 Cont’d: Comparison of clinical features between familial and sporadic psoriatic arthritis

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Sporadic PsA N = 221</th>
<th>Familial PsA N = 150</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF ≥ 70 IU/ml</td>
<td>15</td>
<td>7.8</td>
<td>0.041</td>
</tr>
<tr>
<td>ANA positive</td>
<td>20.4</td>
<td>11.9</td>
<td>0.072</td>
</tr>
<tr>
<td>ESR &gt; 15mm/h</td>
<td>57.2</td>
<td>58.8</td>
<td>0.810</td>
</tr>
<tr>
<td>Medication level (%)</td>
<td></td>
<td></td>
<td>0.001*</td>
</tr>
<tr>
<td>None</td>
<td>52.0</td>
<td>40.3</td>
<td></td>
</tr>
<tr>
<td>ASA, NSAIDs</td>
<td>31.8</td>
<td>40.3</td>
<td></td>
</tr>
<tr>
<td>gold, chloroquine</td>
<td>1.7</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>imuran, methotrexate</td>
<td>7.5</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>PUVA, retinoid</td>
<td>3.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>oral corticosteroids</td>
<td>3.5</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Functional class (%)</td>
<td></td>
<td></td>
<td>0.659*</td>
</tr>
<tr>
<td>grade I</td>
<td>29.5</td>
<td>26.1</td>
<td></td>
</tr>
<tr>
<td>grade II</td>
<td>57.8</td>
<td>64.7</td>
<td></td>
</tr>
<tr>
<td>grade III</td>
<td>11.6</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>grade IV</td>
<td>1.2</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

* reflects overall p-value for the entire group
Table 2: Comparison of HLA antigens between familial and sporadic psoriatic arthritis.

<table>
<thead>
<tr>
<th>HLA antigen</th>
<th>Sporadic PsA N = 173</th>
<th>Familial PsA N = 119</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7</td>
<td>17.3%</td>
<td>17.7%</td>
<td>1.000</td>
</tr>
<tr>
<td>B27</td>
<td>20.8%</td>
<td>22.7%</td>
<td>0.772</td>
</tr>
<tr>
<td>B39</td>
<td>7.5%</td>
<td>5.0%</td>
<td>0.475</td>
</tr>
<tr>
<td>Cw6</td>
<td>14.9%</td>
<td>23.7%</td>
<td>0.083</td>
</tr>
<tr>
<td>DR4</td>
<td>28.9%</td>
<td>26.9%</td>
<td>0.791</td>
</tr>
<tr>
<td>DR7</td>
<td>34.7%</td>
<td>44.5%</td>
<td>0.112</td>
</tr>
<tr>
<td>DQ3</td>
<td>38.4%</td>
<td>44.9%</td>
<td>0.326</td>
</tr>
</tbody>
</table>
Table 3  **Accuracy of proband's self-reported family history**

<table>
<thead>
<tr>
<th>Proband's history</th>
<th>Physician's diagnosis</th>
<th>Physician's diagnosis</th>
<th>Physician's diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Psoriasis</td>
<td>Psoriatic Arthritis</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>63</td>
<td>6</td>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2</td>
<td>25</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>32</td>
<td>12</td>
<td>109</td>
</tr>
</tbody>
</table>
4.3 Part II - Characterization of psoriatic arthritis according to the age of onset of psoriasis.

Background

Discriminating a phenotype based upon the age of onset has rendered some complex diseases into more homogenous groups and subsequently facilitated the identification of disease related genes. For instance, the identification of BRCA1 which is responsible for a proportion of early onset breast cancer and PS1 in early onset Alzheimer's disease has been facilitated by stratifying patients according to the age of onset of the respective diseases (4). Furthermore, segregating psoriasis according to the age of onset has also been quite informative. Epidemiological and clinical studies in psoriasis have shown that the peak age of onset for nonpustular psoriasis, especially the chronic stationary form of the disease, is between 15 and 25 years of age (96). A detailed, retrospective, statistical analysis of 2147 case histories further revealed that the age of onset for psoriasis is bimodally distributed; in approximately two thirds of the cases the peak age of onset was determined to be 16 to 22 years of age, and in the other one third the peak age of onset was determined to be 57 to 60 years of age (97). Patients with early onset psoriasis were more prone to have extensive psoriasis, nail involvement as well as exhibiting a more recurrent form of psoriasis characterized by frequent relapses (73% in early onset vs 27% in late onset group). Almost half of the
patients with early onset psoriasis had first degree relatives who were also affected as compared to 5% of the late-onset group had affected first degree relatives (p< 0.001) (96). Furthermore a strong association of early onset psoriasis and expression of HLA-Cw6 antigen was observed (98).

From these and other observations it has been suggested that there are two distinct subtypes of psoriasis, much the same as there are two distinct subtypes of diabetes. Type I psoriasis is the early onset form of psoriasis which is often associated with a positive family history and generally presents prior to the fourth decade. Type II psoriasis presents with a weaker genetic background and is characterized by onset after the age of 40 years (96). In our previous section we demonstrated that the age of onset of psoriasis and psoriatic arthritis is significantly different between familial and sporadic probands. Therefore there is a strong rationale to look for age-specific effects in psoriatic arthritis. We hypothesized that a more homogenous subset of psoriatic arthritis can be attained by stratifying psoriatic arthritis according to the age of onset of psoriasis. Thus the objective of this study was to characterize psoriatic arthritis probands according to the age of onset of psoriasis.

**Patient selection and methods**

Between January 1, 1978 and June 30 1998, 508 psoriatic arthritis patients were enrolled in the University of Toronto Psoriatic Arthritis Clinic. All patients registered in our clinic were included in the study.
The age of onset of psoriasis was ascertained from each patient at their initial visit to clinic. This was defined as the proband’s first awareness of psoriasis. The age of onset of psoriasis was used to obtain two mutually exclusive groups: early onset (onset of psoriasis less than 40) and late onset (onset of psoriasis ≥ 40). A cut of 40 was chosen for our study based on previous studies from uncomplicated psoriasis (97). In this study by Smith et al, the age of onset of 245 females and 211 males patients with psoriasis was recorded. It was noted that the distribution of age of onset in both sexes is bimodal, with maximum separation at the age of 40 years into an early onset and a late onset group. These distributions were normal (Gaussian) with equal variances. Further evidence for using the age of 40 for a cut off is based on relationship between the age of onset of psoriasis and the number of affected relatives (97). The latter corrected for age at time of study, demonstrates a mixture of two binomial distributions, also with maximum separation at the age of 40 years. Thus the age of 40 years best reflects the bimodality of age of onset psoriasis.

Univariate analysis was used to compare the two groups at their presentation to clinic with respect to: demographics, disease onset and activity, clinical and radiological damage, and functional class. HLA antigens known to be associated with psoriasis and psoriatic arthritis (HLA-B7, HLA-B17, HLA-B27, HLA-B39, HLA-Cw6, HLA-DR4, and HLA-DR7, HLA-DQ3) were also compared (65-72). The majority of the HLA antigens were determined by the
serological method. Continuous variables were compared using the student t-test, while the categorical variables were assessed using a contingency table with chi-squared tests. For categorical variables, if the expected frequencies in any cell were less than 5, Fisher's exact test was used. As this was an exploratory study, corrections were not made for multiple comparisons.

Results

Of the 508 patients with psoriatic arthritis enrolled in our clinic, 397 patients (78%) had an early onset of psoriasis and 111 (22%) had late onset of psoriasis. The mean age at presentation to clinic for the early onset group was 39.7 (sd 12.3) and late onset group was 57.1 (sd 9.3). The differences in the clinical features of early versus late are listed in Tables 4 and 5.

The early onset psoriasis group was more likely to have a self-reported family history of psoriasis (47.2%) than the late onset group (25.2%) (p < 0.001). A similar finding was also noted for psoriatic arthritis (p=0.028). Interestingly, skin lesions were more likely to occur prior to arthritis in the early onset group (p < 0.001). The psoriasis preceded inflammatory arthritis on average by 9.1 years in the early onset group while occurring at the same time in the late onset group (p < 0.001). With respect to the arthritis pattern, the frequency of spondyloarthropathy as a lone feature was similar in both groups. However, the frequency of spondyloarthropathy associated with peripheral arthritis was significantly higher in the early onset group (p < 0.01). There was
no difference noted with respect to arthritis pattern at onset or nail changes. Although the mean number of inflamed joints was higher in late onset (p < 0.01), no differences were noted in the mean number of effusions, clinical or radiological damaged joints, or mean psoriasis area severity index (PASI) score. In addition the medication level, functional class, and laboratory measures were similar.

With respect to HLA antigens, 362/508 (71%) patients had DNA available for comparison. This included 283 probands with early onset psoriasis and 79 with late onset of psoriasis. Differential expression was noted for HLA-B17 and HLA-Cw6 (HLA antigens previously reported to be associated with psoriatic arthritis). These antigens were more frequent in probands with early onset psoriasis. The frequency of HLA-B17 and HLA-Cw6 antigens in the late onset group was similar to that reported in the normal population. HLA-DR7 was more frequent in the late onset psoriasis group.

Discussion

In this study we note a strong familial tendency and predilection for skin lesions to occur prior to arthritis in psoriatic arthritis probands with early onset psoriasis. In addition there is a differential effect of HLA expression depending upon the age of onset of psoriasis.

These observations have important implications regarding the genetic basis for psoriatic arthritis. First of all, it would appear that the individuals with an early onset of psoriasis are more likely to have an affected first degree
relative thus exhibit a greater genetic load for development of psoriatic arthritis. On the basis of the age of onset of psoriasis, we may need to entertain the possibility of two subtypes of psoriatic arthritis, much like psoriasis. An early onset form psoriatic arthritis (where age of onset of psoriasis occurs prior to the age of 40) which is more heritable and exhibits a different HLA antigen distribution. Late onset psoriatic arthritis (where age of onset of psoriasis presents after the age of 40) has a weaker familial tendency and less likely to be associated with HLA antigens previously known to be associated with psoriasis or psoriatic arthritis from previous studies. However the difference in clinical expression between these groups in psoriatic arthritis is not as striking as in uncomplicated psoriasis. Furthermore a substantial proportion of patients with late onset psoriasis have a family history of psoriasis (25%). Thus further studies are needed with a larger number of patients, prior to establishing two different subsets of psoriatic arthritis. However for the time being it may be prudent to stratify families in a linkage study based on the age at onset in linkage studies, as a differential degree of heritability and HLA expression have been noted. Furthermore, the age of onset of psoriasis in psoriatic arthritis can be utilized to calculate more precise familial recurrence estimates for genetic modeling in gene identification studies.

A limitation of this study has to do with the accuracy of reporting the first occurrence of psoriasis by the proband. The accuracy of the proband's reporting the age of onset of psoriasis has been previously assessed by
inspecting the age of onset distribution curve (97). It was concluded that before the age of 10 the probands were accurate in identifying the onset of psoriasis to within a year, between the ages of 10 and 20 years the accuracy was within two years, while later in life there is a tendency to round off the age of onset to a multiple of 5 years. The accuracy of the age of onset of psoriasis will also depend on the duration of psoriasis prior to presentation to clinic. In the present study the early onset group had onset of psoriasis on average 17 years prior to presentation to clinic as compared to 7 years for the late onset group (p < 0.001). Thus the history regarding the onset of psoriasis may be more erroneous in the early onset group. Despite this limitation, dermatologists have noted patients are able to detect the presence of psoriasis as well as assess its severity with a fair degree of accuracy (99).

As this was an exploratory study no attempts were made to correct for the multiple comparisons. Therefore, caution must be exercised in interpreting these data as noted in the discussion in Part I of the thesis. Furthermore, with respect to the HLA antigens, the study may have lacked enough power to detect differences, given the infrequent occurrence of some of the HLA antigens.

The phenotype was split according to age of onset of psoriasis rather than the age of psoriatic arthritis, as it was felt that patients can more accurately determine the onset of a new skin eruption rather than inflammatory arthritis. This is clinically reflected by the fact that the age at first diagnosis
rather than onset of symptoms is often quoted by the patient when they are asked regarding the onset of inflammatory arthritis. As stated in the methods, the rationale for using the age of 40 as a cut off to distinguish early versus late onset psoriasis was based on previous studies with psoriasis that noted a maximal difference in clinical features and heritability when the onset of psoriasis was stratified at 40.

In light of our findings, the age of onset of psoriasis may need to be considered as a potential stratifying variable in future immunogenetic and linkage studies. Inclusion of the age of onset of psoriasis a priori as a potential stratification variable, will likely reduce the inherent heterogeneity of psoriatic arthritis in linkage studies.
Table 4: Comparison of PsA patients with early (< 40 yrs) versus late (>40 yrs) onset psoriasis

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>&lt; 40 years</th>
<th>≥ 40 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>N = 397</td>
<td>N = 111</td>
<td></td>
</tr>
<tr>
<td>age at presentation to clinic (yrs); mean, sd</td>
<td>39.7 (12.3)</td>
<td>57.1 (9.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>gender: % male</td>
<td>56.7</td>
<td>49.5</td>
<td>0.182</td>
</tr>
<tr>
<td>race: % Caucasian</td>
<td>94</td>
<td>96</td>
<td>1.000</td>
</tr>
<tr>
<td>Family Hx - psoriasis (%)</td>
<td>47.2</td>
<td>25.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Family Hx - PsA (%)</td>
<td>12.9</td>
<td>5.4</td>
<td>0.028</td>
</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>skin lesion prior to arthritis (%)</td>
<td>81.3</td>
<td>48.6</td>
<td>0.001</td>
</tr>
<tr>
<td>nail changes (%)</td>
<td>62.0</td>
<td>62.2</td>
<td>0.970</td>
</tr>
<tr>
<td>Arthritis pattern at onset (%)</td>
<td></td>
<td></td>
<td>0.547*</td>
</tr>
<tr>
<td>distal</td>
<td>17.9</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>oligoarthritis</td>
<td>29.0</td>
<td>28.2</td>
<td></td>
</tr>
<tr>
<td>polyarthritis</td>
<td>30.0</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>back only</td>
<td>4.9</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>back + distal</td>
<td>2.8</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>back + oligoarthritis</td>
<td>4.9</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>back + 3 polyarthritis</td>
<td>10.5</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Extra-articular features (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tendinitis</td>
<td>29.3</td>
<td>27.3</td>
<td>0.820</td>
</tr>
<tr>
<td>mucus membrane lesions</td>
<td>15.7</td>
<td>20.5</td>
<td>0.288</td>
</tr>
<tr>
<td>urethritis</td>
<td>5.2</td>
<td>5.9</td>
<td>1.000</td>
</tr>
<tr>
<td>iritis/conjunctivitis</td>
<td>5.0</td>
<td>9.0</td>
<td>0.117</td>
</tr>
<tr>
<td>malaise</td>
<td>15.3</td>
<td>24.3</td>
<td>0.027</td>
</tr>
<tr>
<td>diarrhea</td>
<td>0.5</td>
<td>0.9</td>
<td>0.524</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of active joints (mean, sd)</td>
<td>9.2 (8.7)</td>
<td>12.0 (10.5)</td>
<td>0.010</td>
</tr>
<tr>
<td># of effusions (mean, sd)</td>
<td>2.5 (3.3)</td>
<td>2.9 (3.8)</td>
<td>0.260</td>
</tr>
<tr>
<td>PASI score (mean, sd)</td>
<td>6.6 (8.2)</td>
<td>5.1 (7.6)</td>
<td>0.387</td>
</tr>
<tr>
<td>Clinical damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of deformed joints (mean, sd)</td>
<td>3.0 (7.0)</td>
<td>3.5 (8.0)</td>
<td>0.540</td>
</tr>
<tr>
<td>Radiological damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of joints &gt; stage 2 (mean, sd)</td>
<td>5.0 (8.2)</td>
<td>5.3 (8.1)</td>
<td>0.671</td>
</tr>
</tbody>
</table>

*reflects overall p-value for the entire group
Table 4 Cont’d Comparison of PsA patients with early (< 40 yrs) versus late (>40 yrs) onset psoriasis

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>&lt; 40 years</th>
<th>&gt; 40 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 397</td>
<td>N = 111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF ≥ 70 IU/ml (%)</td>
<td>11.2</td>
<td>11.8</td>
<td>0.850</td>
</tr>
<tr>
<td>ANA positive (%)</td>
<td>20.1</td>
<td>24.8</td>
<td>0.341</td>
</tr>
<tr>
<td>ESR &gt; 15mm/h (%)</td>
<td>56.4</td>
<td>64.5</td>
<td>0.111</td>
</tr>
<tr>
<td>Medication level (%)</td>
<td></td>
<td></td>
<td>0.081*</td>
</tr>
<tr>
<td>None</td>
<td>49.6</td>
<td>44.1</td>
<td></td>
</tr>
<tr>
<td>ASA, NSAIDs</td>
<td>33.0</td>
<td>37.8</td>
<td></td>
</tr>
<tr>
<td>gold, chloroquine</td>
<td>4.5</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>imuran, methotrexate</td>
<td>8.3</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>PUVA, retinoid</td>
<td>2.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>oral corticosteroids</td>
<td>2.0</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with grades III and IV</td>
<td>10.3</td>
<td>16.2</td>
<td>0.087</td>
</tr>
</tbody>
</table>

* reflects overall p-value for the entire group
Table 5 - Comparison of HLA antigens in PsA patients with early onset psoriasis (< 40 years) and late onset of psoriasis (> 40 years)

<table>
<thead>
<tr>
<th>HLA antigen</th>
<th>Early Onset N = 283</th>
<th>Late Onset N = 79</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7</td>
<td>6.0%</td>
<td>7.6%</td>
<td>0.609</td>
</tr>
<tr>
<td>B17</td>
<td>22.6%</td>
<td>5.1%</td>
<td>0.001</td>
</tr>
<tr>
<td>B27</td>
<td>21.2%</td>
<td>25.3%</td>
<td>0.436</td>
</tr>
<tr>
<td>B39</td>
<td>6.7%</td>
<td>6.35%</td>
<td>0.903</td>
</tr>
<tr>
<td>Cw6</td>
<td>21.2%</td>
<td>11.3%</td>
<td>0.063</td>
</tr>
<tr>
<td>DR4</td>
<td>27.7%</td>
<td>29.1%</td>
<td>0.799</td>
</tr>
<tr>
<td>DR7</td>
<td>40.8%</td>
<td>25.3%</td>
<td>0.012</td>
</tr>
<tr>
<td>DQ3</td>
<td>38.4%</td>
<td>44.9%</td>
<td>0.326</td>
</tr>
</tbody>
</table>
4.4 Part III Parent of origin effect in psoriatic arthritis

Background

Psoriatic arthritis, much like uncomplicated psoriasis and other autoimmune disorders, belongs to the category of complex non-Mendelian diseases. For this reason, misclassification of clinical phenotypes, incomplete penetrance, variable expression, and genetic heterogeneity will likely complicate the detection of gene(s) for psoriatic arthritis (5). Recent studies in selected autoimmune diseases has identified another potential factor which may need to be accounted for in genetic mapping of psoriatic arthritis (78). This is the differential expression of a disease depending on the gender of the disease transmitting parent (88). This phenomenon has not been investigated in psoriatic arthritis. We hypothesized that a differential transmission of psoriatic arthritis exists at the phenotypic level depending on the gender of the affected parent. This hypothesis was tested by assessing the differential penetrance and expression of psoriatic arthritis depending upon maternal as compared to paternal transmission.

Patient selection and methods
Part A - Disease Transmission
1) All probands with a parental history of psoriasis or psoriatic arthritis were identified from the University of Toronto Psoriatic Arthritis Clinic, in order to detect differences in parental transmission of psoriatic arthritis.

2) All offspring from our probands were identified in order to determine differences in transmission between male and female probands to an affected offspring.

3) All probands with clinically unaffected parents but with an affected second degree relative (grandparents, aunts or uncles) were identified in order to detect any differences in transmission of psoriatic arthritis between maternal and paternal relations.

Part B - Disease expression

Difference in expression of psoriatic arthritis in probands with paternal versus maternal transmission, were evaluated at the proband's presentation to clinic. The two groups were compared with respect to demographics, disease onset and activity, clinical and radiological damage, functional class, and laboratory features. The groups were also compared with respect to the HLA antigens known to be associated with psoriasis or psoriatic arthritis which include: HLA-B7, HLA-B17, HLA-B27, HLA-B39, HLA-Cw6, HLA-DR4, and HLA-DR7 (65-72).
Analysis

The normal approximation to the binomial distribution was used to obtain standard deviations of the observed proportions and to test if the proportions of probands with maternal versus paternal history were different from 0.5. A similar analysis was used to compare affected second degree relatives of maternal versus paternal lineage. The frequency of affected offspring (psoriasis or psoriatic arthritis) between male and female probands were compared using normal approximation to the binomial. The variables for the expression of maternal versus paternal psoriatic arthritis were compared using a t-test for continuous variables and Fisher’s exact test for categorical variables.

Results

Five-hundred and eight patients registered in our clinic were enrolled in the study. This included 228 females males (44.9%) and 280 (55.1%) males. Ninety-six percent of the patients were Caucasians, 1% African Americans and 3% represented other ethnic groups. The mean age of patients at presentation to our clinic was 43.5 years (sd 15.4) and at the time of the study was 56.0 years (sd 12.2). The mean age of onset of psoriasis and psoriatic arthritis were similar for male and female probands: 28.3 versus 28.9 years, (p=0.629) for psoriasis; and 35.5 versus 36.2 years, (p=0.563) for psoriatic arthritis.
Part A)

1) Ninety-five probands had an affected parent (psoriasis or psoriatic arthritis). Sixty-two of these probands (65%) had an affected father as compared to 33 probands (35%) with an affected mother. Thus the proportion of paternal transmission (0.65) was significantly greater than the expected proportion of 0.5 (p=0.001).

2) Thirty-five male probands and 43 female probands had offspring. Twelve of the seventy-four offspring (16.2%) from male probands were affected with either psoriasis or psoriatic arthritis as compared to 9 out of 108 offspring (8.3%) of female probands (p=0.10).

3) Thirty-four probands were identified with an affected second degree relative but with no affected first degree relatives. In these families, the parent related to the affected relative is presumed to be the carrier of the potential psoriatic arthritis gene(s). In 21 (62%) of these probands the affected relatives descended from the paternal side of the family as compared to 13 (38%) probands from the maternal side (p=0.17).

Although there was a slight excess in favor of father to son transmission as compared to father to daughter (53% vs 47% respectively, p=0.72) and mother to daughter transmission as compared to mother to son transmission (55 vs 45%, p=0.59), these differences did not reach statistical significance.
Part B)

With respect to disease expression between paternal (n= 62) and maternal (n = 33) transmitted psoriatic arthritis there was no difference in the probands with respect to mean age of onset of arthritis (32.7 years (sd 11.2) versus 34.5 years (sd 13.6); p=0.49), age at onset of psoriasis (22.6 years (11.8) versus 25.5 years (11.7); p=0.25), and age at presentation to clinic (38.7 years (sd 10.6) versus 42.7 years (sd 14.0); p=0.12) respectively (Table 6). There was also no difference detected regarding the severity of inflammatory arthritis (as assessed by the number of actively inflamed joints, clinical and radiological damage), psoriasis (as assessed by PASI), medication usage, or functional class at presentation to clinic. However paternally transmitted subjects had higher frequency of skin lesions prior to arthritis (p=0.047), erythrocyte sedimentation rate (ESR) > 15mm/h (p=0.044), and a lower prevalence of rheumatoid factor (p=0.044). There was no difference noted in the frequencies of HLA antigens which have been previously shown to be associated with psoriasis or psoriatic arthritis (Table 7). As this was an exploratory analysis no corrections were made for multiple comparisons when assessing disease expression between male and female probands. If multiple testing were to be accounted for, these differences would not reach statistical significance.

Discussion
The present study demonstrates an excess paternal transmission of psoriatic arthritis. This is most convincingly demonstrated with respect to parental history of the proband. The probands in our sample were much more likely to have an affected father. A similar trend of excess paternal transmission was noted in the offspring of male probands but this did not reach statistical significance at the 5% level, likely due to the relatively small number of offspring available. The evaluation of second degree relatives is interesting from at least two points of view. The significantly higher rate of psoriatic arthritis in the second degree relatives in comparison to the population rate favors the idea of genetic susceptibility of psoriatic arthritis as second degree relatives are less likely to share a similar environment. Secondly, the fact that there are more probands with affected paternal than maternal relatives, supports the main finding of the present study that genetic factors predisposing to psoriatic arthritis are more penetrant if inherited from the father.

Skin lesions prior to arthritis, an elevated ESR and the presence of rheumatoid factor were the only clinical or laboratory differences noted between probands of maternal versus paternal transmitted disease. Of particular importance, the age at onset of psoriatic arthritis and disease severity were similar in both groups.

Genetic information passed through the nucleus consists of genetic factors in the form of DNA base sequences and epigenetic DNA modification (100). One of the epigenetic mechanisms is genomic imprinting and it refers to
the differential expression of a disease depending upon the sex of the parent transmitting genes predisposing to a disease. An understanding of the mechanism behind genetic imprinting remains elusive with methylation being the most popular mechanistic explanation (101).

The preferential transmission of disease from parents of a particular sex to a child is classically demonstrated in several rare genetic syndromes such as Angelman and Prader-Willi (102). Parent of origin effect has been detected in Mendelian diseases such as Huntington's disease, cystic fibrosis, and myotonic dystrophy, however the molecular mechanism of such imprinting is unclear (102). There is a growing list of autoimmune disorders which appear to have differential expression depending on the sex of the affected parent (103-105). Based on clinical studies, two independent lines of evidence exist for genomic imprinting in psoriasis (100,106). These include an increased preponderance of inheritance of psoriasis from the father (65%) over the mother (35%) (p < 0.001). Secondly, the birth weight of children from parents with psoriasis is influenced by the sex of the psoriatic parent as the infants from male probands were 270 gram heavier than female probands (p=0.004). Other autoimmune disorders that exhibit differential expression depending upon the sex of the affected parent include insulin dependent diabetes mellitus, inflammatory bowel disease, asthma and rheumatoid arthritis (99,103-104).
At the molecular level the parent of origin effect has been studied for certain of these autoimmune disorders. We recently determined that linkage to rheumatoid arthritis demonstrates parent of origin effects at the MHC region in the short arm of chromosome 6p, by using data available from a recent genome scan in 90 Caucasian European families (104). In our study, maternal and paternal alleles shared identical by descent by affected sibling pairs with rheumatoid arthritis were observed, and deviations from the null hypothesis of no linkage were examined (105). A number of markers demonstrated differences in the parental origin of shared alleles in affected sib pairs suggesting that parental specific effects may be important for some genes which increase susceptibility to rheumatoid arthritis. Multipoint analysis at a marker of chromosome 6p (D6S455) showed evidence for linkage of maternal, but not paternal meioses. This is likely due to parent of origin effects in this region although this could partly be due to sex differences in genetic maps in this region.

Furthermore, a recent linkage study in psoriasis, using sibling pairs noted an excess transmission of microsatellite markers and greater evidence of linkage when the allele was of paternal origin. The preference for excess paternal transmission in psoriasis is in keeping with our clinical findings in psoriatic arthritis. Excess transmission of paternal HLA alleles as compared to maternal transmission has also been described in diabetes but this has not been replicated in other samples (107). The differences across various studies
are not surprising because mechanisms of genomic imprinting may be very complicated and would require large sample sizes and more sophisticated analytical approaches. A good example comes from the insulin gene (INS) studies in IDDM. When INS was subjected to parent of origin analyses in IDDM, and similarly to HLA analyses, the various groups investigating this phenomenon reported different results (108-112). The discrepancies for the parent of origin effect at the INS gene region were resolved only after the role of the untransmitted parental allele was detected (108,113).

Further molecular evidence of the potential imprinting in the HLA region is suggested from animal models. The major histocompatibility complex (MHC) in chromosome 17 in mice is syntenic to MHC complex in chromosome 6p in humans. Molecular studies in mice suggest that MHC region in chromosome 17 in mice appears to be an imprinted region (114,115).

Before concluding that a parent of origin effect exists in psoriatic arthritis the scheme used to ascertain family data must be examined. If one is not aware of resulting biases, a given disorder may mimic some of the features of non-Mendelian inheritance. Ottman et al. (116) provide an example from their study of the inheritance of epilepsy where they ascertained probands and the affected status of the offspring from medical records. Unfortunately histories of epilepsy in mothers are routinely included in obstetric records, while those in fathers are not. This method of data collection led to a better ascertainment of offspring of affected mothers than of affected fathers resulting in a sample that
looked like excess maternal inheritance. In our study, the ascertainment of the relative’s phenotype (the proband’s parents, children or second degree relative) was based on the proband’s self reported history. The diagnosis of psoriasis or psoriatic arthritis in these relatives was not confirmed in our clinic. Although this is a potential limitation of our study, as noted in Part I, the probands were quite accurate regarding the affection status of their relatives. Even if the true incidence of familial psoriasis is underestimated somewhat, this should not result in an excess of paternal transmission as we did not selectively ascertain sex-specific parent-child pairs. Thus the reliance upon the proband’s self-reported history does not invalidate our conclusions. Secondly, there was no age at onset differences between males and females. Thus the preferential paternal transmission noted in our study is unlikely to be due to an ascertainment bias on this basis.

In our study we demonstrated an excess paternal transmission primarily on the basis of a differential parental transmission to the proband. If it is assumed that a parent of origin effect exists in psoriatic arthritis one would predict that the offspring and second degree relatives of male probands with psoriatic arthritis would more likely be affected with either psoriatic arthritis or psoriasis than female probands with psoriatic arthritis. We noted an excess paternal transmission in the proband’s offspring and second degree relatives. Furthermore the percentage of excess parental transmission was similar in all three groups (parents 65%; offspring 66%; second degree relatives 62%).
The consistency and extent of excess paternal transmission in all three groups suggests that the lack of statistical significance in offspring and second degree relatives is likely due to an inadequate sample size.

The observation of excess paternal transmission is inconsistent with mitochondrial inheritance, as this mode of inheritance usually leads to excess maternal inheritance. Given the lack of any plausible mechanism for anticipation in psoriatic arthritis and the problems with respect to ascertainment biases in conducting studies to determine the presence of anticipation, the presence for this phenomenon was tested in our study. Furthermore, clinical information with respect to the age of onset and severity of psoriatic arthritis was not recorded for proband's parents or offspring.

In conclusion, there appears to be an excess paternal transmission in psoriatic arthritis. Thus the susceptibility to psoriatic arthritis may involve a gene or genes modified during gametogenesis. Further clinical confirmation and elucidation of the genetic basis of parent of origin effect is warranted as this phenomenon may need to be accounted for when determining the optimal model of disease transmission in psoriatic arthritis.
Table 6: Comparison of PsA patients with paternal versus maternal history of psoriasis

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Paternal history</th>
<th>Maternal history</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 62</td>
<td>N = 33</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age at clinic presentation (yrs); (mean, sd)</td>
<td>38.7 (10.6)</td>
<td>42.7 (14.0)</td>
<td>0.1189</td>
</tr>
<tr>
<td>gender: % male</td>
<td>66.1</td>
<td>60.6</td>
<td>0.593</td>
</tr>
<tr>
<td>race: % Caucasian</td>
<td>88.9</td>
<td>100</td>
<td>1.000</td>
</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age at onset of psoriasis (yrs, sd)</td>
<td>22.6 (11.8)</td>
<td>25.5 (11.7)</td>
<td>0.492</td>
</tr>
<tr>
<td>age at onset of arthritis (yrs, sd)</td>
<td>32.7 (11.2)</td>
<td>34.5 (13.6)</td>
<td>0.256</td>
</tr>
<tr>
<td>skin lesion prior to arthritis (%)</td>
<td>88.7</td>
<td>72.7</td>
<td>0.047</td>
</tr>
<tr>
<td>Arthritis pattern at onset (%)</td>
<td></td>
<td></td>
<td>0.365*</td>
</tr>
<tr>
<td>distal</td>
<td>16.4</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>oligoarthritis</td>
<td>29.5</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>polyarthritis</td>
<td>31.2</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>back only</td>
<td>4.9</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>back + distal</td>
<td>4.9</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>back + oligoarthritis</td>
<td>9.8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>back + polyarthritis</td>
<td>3.3</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of active joints (mean, sd)</td>
<td>7.9 (7.0)</td>
<td>8.3 (7.1)</td>
<td>0.823</td>
</tr>
<tr>
<td># of effusions (mean, sd)</td>
<td>1.6 (2.5)</td>
<td>2.2 (2.4)</td>
<td>0.285</td>
</tr>
<tr>
<td>PASI score (mean, sd)</td>
<td>6.4 (7.6)</td>
<td>6.6 (8.8)</td>
<td>0.969</td>
</tr>
<tr>
<td>Clinical damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of deformed joints (mean, sd)</td>
<td>1.3 (3.3)</td>
<td>3.6 (9.2)</td>
<td>0.1698</td>
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<tr>
<td>Radiological damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of joints &gt; stage 2 (mean, sd)</td>
<td>2.3 (4.0)</td>
<td>5.7 (10.0)</td>
<td>0.0739</td>
</tr>
</tbody>
</table>

*reflects overall p-value for the entire group using chi-square test
Table 6 Cont’d: *Comparison of PsA patients with paternal versus maternal history of psoriasis*

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Paternal history</th>
<th>Maternal history</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 62</td>
<td>N = 33</td>
<td></td>
</tr>
<tr>
<td>Laboratory values (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rheumatoid factor</td>
<td>1.7</td>
<td>12.9</td>
<td>0.044</td>
</tr>
<tr>
<td>anti-nuclear antibody</td>
<td>18.8</td>
<td>3.8</td>
<td>0.090</td>
</tr>
<tr>
<td>ESR. # &gt; 15 mm/h</td>
<td>58.1</td>
<td>36.4</td>
<td>0.044</td>
</tr>
<tr>
<td>Medication level (%)</td>
<td></td>
<td></td>
<td>0.065*</td>
</tr>
<tr>
<td>None</td>
<td>45.2</td>
<td>48.5</td>
<td></td>
</tr>
<tr>
<td>ASA, NSAIDs</td>
<td>45.2</td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td>gold, chloroquine</td>
<td>1.6</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>imuran, methotrexate</td>
<td>8.1</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>PUVA, retinoid</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>oral corticosteroids</td>
<td>0</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with grades III and IV</td>
<td>6.5</td>
<td>9.1</td>
<td>0.691</td>
</tr>
</tbody>
</table>

* reflects overall p-value for the entire group using chi-square test
Table 7 - Comparison of HLA antigens in PsA patients with paternal versus maternal history of psoriatic arthritis

<table>
<thead>
<tr>
<th>HLA antigen</th>
<th>Paternal transmission N = 36</th>
<th>Maternal transmission N = 26</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7</td>
<td>2.8%</td>
<td>7.7%</td>
<td>0.567</td>
</tr>
<tr>
<td>B17</td>
<td>27.8%</td>
<td>19.2%</td>
<td>0.601</td>
</tr>
<tr>
<td>B27</td>
<td>5.6%</td>
<td>19.2%</td>
<td>0.119</td>
</tr>
<tr>
<td>B39</td>
<td>8.4%</td>
<td>3.8%</td>
<td>0.630</td>
</tr>
<tr>
<td>Cw6</td>
<td>33.3%</td>
<td>16.7%</td>
<td>0.135</td>
</tr>
<tr>
<td>DR4</td>
<td>25.0%</td>
<td>26.9%</td>
<td>0.864</td>
</tr>
<tr>
<td>DR7</td>
<td>39.0%</td>
<td>35.3%</td>
<td>0.794</td>
</tr>
<tr>
<td>DQ3</td>
<td>47.2%</td>
<td>42.3%</td>
<td>0.701</td>
</tr>
</tbody>
</table>
Psoriatic arthritis is a complex trait. The etiology of psoriatic arthritis is likely due an interplay of one or more genetic and/or environmental factors and not to attributes of a single gene. At present time, there is compelling epidemiological and immunogenetic evidence to indicate that susceptibility of psoriatic arthritis is inherited. As a result further elucidation of its genetic basis will be enhanced by a positional cloning strategy. Geneticists have made substantial progress in elucidating the genetic basis of numerous single gene disorders using this approach. The detection of genetic factors for complex traits will be far more complicated given the added complexities in multifactorial disorders. This includes sub-optimal analytical methods in the identification of
susceptibility regions in complex traits as the genetic analysis in complex
diseases has lagged behind those of single-gene Mendelian traits.

The use of binary "affected" or "unaffected" phenotypes may not be
particularly powerful in complex traits, and instead subgroups of the phenotype
may be more useful for genetic studies since it is likely that the genes
underlying such traits are fewer and the effect sizes of at least some loci are
likely to be larger. In addition an added complication arises in the presence of
a multiple disease causing mutation since the selection of the initial candidate
gene for the sequence analysis will be instrumental to the success of
functional studies. Clinical studies may implicate certain functional or
expressional changes if the mutation itself contributed to the variation of the
phenotype in question. Mutations that have frequency distribution that are most
concordant with the phenotype (especially with unrelated affected individuals)
are often considered to be the best candidates. An irrelevant nonsynonymous
mutation can be ruled out largely due to evolutionary factors, as they are likely
to disrupt the accidental and false concordance between polymorphism
distribution and the phenotypic differences. Therefore the dissection of
phenotypes may be of relevance as it may direct future studies to the
candidate loci with the strongest genetic contribution.

Optimal design of a linkage study will also depend to some extent on
the precise nature of the genetic complexities to be surmounted. One such
complexity is multiple loci causing a heterogeneous disorder. Often these
details cannot be known with precision in advance. Therefore one ought to begin searching for the genetic basis of a complex disease by enumerating the likely range of complexities, based on the available evidence.

Identification of the specific genetic component involved in a trait will aid in development of a mathematical model for transmission of disease. Schork and Guo (117) presented a variety of likelihood-based models that account for the properties of mitochondrial genetics. A similar framework has been presented by Risch (118) using empirical risk ratio patterns among different relative types to obtain information about specific models. If the assumptions about the genetic etiology are correct, one will enhance the prospects of positional cloning to identify susceptibility genes. Therefore population based studies may contribute significantly with respect to a successful linkage study. Furthermore clinical confirmation of modes of transmission implicating genomic imprinting will direct further studies regarding the elucidation of this mechanism. If this is a true phenomenon, inevitably molecular alterations accounting for the imprinting will be found. This may help to partially explain the differential phenotypic expression of various simple and complex genetic disorders.

In this thesis we investigated ways to minimize the genetic heterogeneity using a very well characterized population of psoriatic arthritis patients. Our first approach was to identify potential features which can subsequently be used to split a heterogeneous disease based on clinical and/or biological
properties. To do this we compared probands with familial versus sporadic psoriatic arthritis (Part I). From this study we concluded that familial cases had a significantly earlier age of onset. Trends in other clinical and immunogenetic features were also noted.

Based on the results of our initial study we felt that there was a strong rationale to look for age specific effects in psoriatic arthritis. Therefore in Part II we further characterized psoriatic arthritis according to the age of onset of psoriasis. We noted a differential expression of clinical features and HLA antigens depending upon the age of onset of psoriasis. Early onset psoriatic arthritis patients demonstrate a stronger association with known HLA antigens than the late onset group. Therefore early onset of psoriasis in patients with psoriatic arthritis patients be a more homogeneous subset. Thus it is conceivable that affected relatives with early onset psoriasis may be linked to particular chromosomal regions that are not present in late onset psoriasis in patients with psoriatic arthritis. As a result, age of onset of psoriasis should be considered as a potential stratification variable a priori, in order to reduce the genetic heterogeneity of psoriatic arthritis. Our study suggests that sibling pairs with early onset psoriasis may be the most informative family structure in elucidating the genetic basis of psoriatic arthritis.

In part III we assessed the parent of origin effect in psoriatic arthritis at the phenotypic level. The overall methodological approach was to compare the difference in penetrance and expression of psoriatic arthritis in offspring of an
affected mother versus an affected father. This study demonstrated an excess paternal transmission in psoriatic arthritis. Issues concerning possible ascertainment biases that can potentially lead to non-Mendelian patterns were reviewed and appear not to be a major confounder in our study. Therefore the inclusion of the parent of origin effect in the genetic modeling for disease transmission may lead to further reduction in the genetic heterogeneity of a complex trait.

As we are the first investigators to perform these studies regarding the genetic epidemiology of psoriatic arthritis, it can be concluded that the identification of a more homogenous subset and understanding of the biological properties of disease transmission is just beginning. Development of approaches to account for phenomena such as age- and parent-specific effects is a relatively new area of research. Awareness of these characteristics will likely be quite important in the delineation of the genetic basis of psoriatic arthritis. We speculate that noting such variables a priori may assist in the fine mapping and ultimate cloning of susceptibility loci for this complex disease. Therefore the findings from this thesis will facilitate future linkage studies in psoriatic arthritis. If this approach is successful in elucidating the genetic basis of psoriatic arthritis, these methods can be adopted for other complex rheumatic traits.
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