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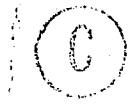
THE UNIVERSITY OF ALBERTA

THE IMMUNOGENETICS OF PSORIASIS: RELATIONSHIP TO SPONDYLITIS, HLA-B27 AND HAPLOTYPE INHERITANCE

BY

MARIA E. SUAREZ-ALMAZOR



A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled The Immunogenetics of Psoriasis: Relationship to Spondylitis, HLA-B27 and Haplotype Inheritance submitted by Maria E. Suarez-Almazor in partial fulfilment of the requirements for the degree of Master of Science.

Dr. Anthony S. Russell
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Dr. Stephen Aaron

Dr. Michael Grace

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To my husband, Eduardo, and our children, Eduardo Jr., Sofia and Sebastian.

ABSTRACT

The purpose of our research was to clarify some aspects related to the immunogenetics of psoriasis and psoriatic arthritis. We conducted three separate studies.

1. HLA Study: B27 and Psoriasis. The aim of this study was to determine the characteristics of spinal involvement in psoriasis and its relationship to HLA-B27 and peripheral arthritis. One hundred eighty-one patients attending a dermatology clinic (PUVA or general dermatology clinic) were included. Twenty-two (12%) were B27 positive. Twenty had peripheral psoriatic arthritis; 3 of these showed sacroiliitis (1 B27 positive, 2 B27 negative). Only 1 of the other 161 patients had sacroiliitis and he was B27 positive. Subsequently we examined 54 consecutive patients attending the Rheumatic Disease Unit at the University of Alberta. All patients had a definite diagnosis of psoriatic arthritis; 51 had peripheral arthritis (6 with sacroiliitis) and 3 exclusive axial involvement (2 sacroiliitis, 1 typical syndesmophytes with normal sacroiliac joints). Patients from the dermatology and rheumatology clinics were pooled together and divided in 4 groups: B27 positive and negative, with or without peripheral arthritis. Spinal arthritis was observed mainly in the group of patients with both HLA-B27 and peripheral arthritis (23.5%).

HLA-B27 and/or peripheral arthritis were associated with an increase in axial involvement. Patients lacking both B27 and peripheral arthritis seldom developed spinal disease (0.7%). Half of the patients with peripheral arthritis and spinal involvement were B27 positive. All 3 B27 positive patients without peripheral arthritis and with spinal disease were male and they all had bilateral sacroiliits and indistinguishable from idiopathic ankylosing spondylitis (AS).

HLA-B27 and peripheral arthritis appeared to act as separate factors that increased the risk of spinal arthritis in patients with psoriasis. The effect of B27 on psoriasis appeared to be detected in two different ways: as a coincidental factor increasing the risk of idiopathic AS (as for the general population) or as one of the multiple HLA associations that increase the risk of psoriatic arthritis; in this latter case the spinal involvement would occur as another manifestation of the clinical course of the disease.

2. Sibship Study. The purpose of this study was to determine whether the inheritance of psoriasis was HLA linked. We studied 12 families with at least 2 siblings with psoriasis. We used a sib pair analysis comparing the HLA haplotypes in affected siblings of these families. Haplotype sharing was analyzed in 15 sib pairs; expected frequencies of haplotype sharing were estimated as 25% for HLA identity and 50% for haplo

identity. All sib pairs shared at least 1 haplotype and 13 of the 15 were HLA identical compared to the expected frequency of 4 ($p < 0.01$). These results suggest that more than one HLA linked gene is implicated in the development of psoriasis.

3. B27 Positive Family Study. The purpose of this study was to examine the segregation patterns in families with psoriasis, ankylosing spondylitis and HLA-B27 and determine the relationship and/or linkage between these three factors. Five families were included: all of them had at least one B27 haplotype and family members with psoriasis and/or ankylosing spondylitis. In all 5 families the segregation of psoriasis and typical ankylosing spondylitis appeared to be independent, thus, patients with both psoriasis and HLA-B27 had relatives with ankylosing spondylitis carrying the B27 antigen and relatives with psoriasis carrying the non B27 haplotype. In some cases family members combined all three factors and had both AS and psoriasis with a positive HLA B27. Only in 1 case two different haplotypes appeared to be related to psoriasis. This occurred, however, in two cousins.

Our results suggest that although spinal involvement is a frequent feature in psoriatic arthritis, in general psoriasis and typical B27 positive ankylosing spondylitis are two separate disorders.

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ABBREVIATIONS

AAU: Acute Anterior Uveitis

AS: Ankylosing Spondylitis

Asym SI: Asymmetric Sacroiliitis

cM: Centimorgan

Derm: Dermatololgy

HLA: Human Leukocyte Antigens

Ig: Immunoglobulin

JRA: Juvenile Rheumatoid Arthritis

MHC: Major Histocompatibility Complex

MW: Molecular Weight

NA: Not Available

Per Ar: Peripheral Arthritis

PUVA: Psolaren Ultraviolet A

RA: Rheumatoid Arthritis

RDU: Rheumatic Disease Unit

RFLP: Restriction Fragment Length Polymorphism

SD: Standard Deviation

SI: Sacroiliitis

CHAPTER 1

INTRODUCTION

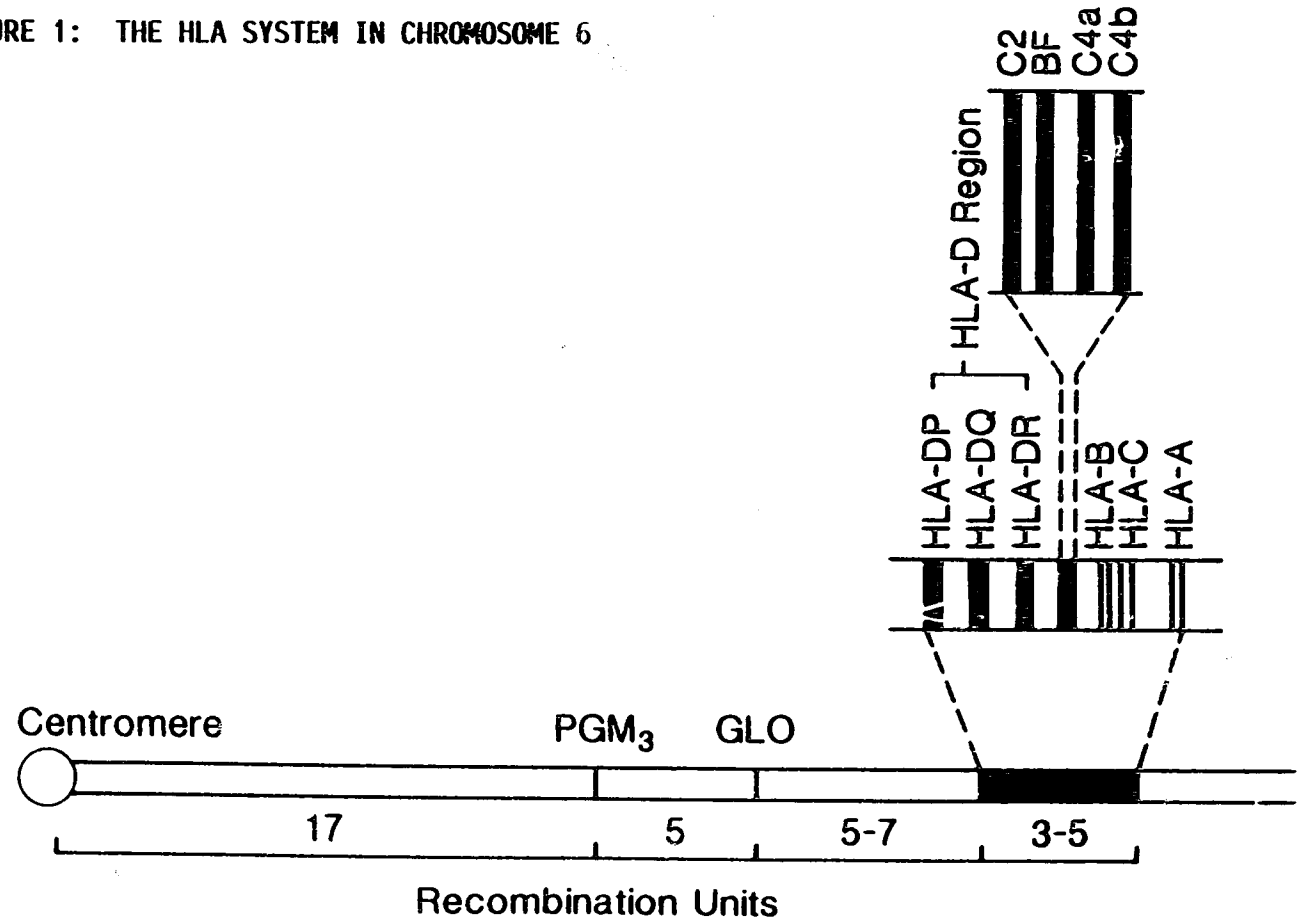
1. HLA AND DISEASE

Since the description of the first association between a human histocompatibility marker and a disease, Hodgkin's lymphoma,[1] great emphasis has been placed in the finding of new linkages between the major histocompatibility complex and a variety of disorders.[2] This has been of particular importance in the case of the so-called "autoimmune" diseases, especially in rheumatology, where several associations have been described.[3,4] In most cases the etiology of these disorders is still unknown, however, their linkage to the MHC has led to a new approach in the clinical, genetic and basic research related to them. These associations have been particularly relevant in several aspects that include: diagnosis, selection of individuals at risk, in particular relatives of affected patients, and search of specific pathogenetic mechanisms.

A. THE HLA SYSTEM: DESCRIPTION

The human MHC is the HLA (human leukocyte antigen) system. Its genes are located on the short arm of chromosome 6 within a distance of 3-5 cM (Figure 1). According to differences in structure and function, the MHC products can be classified in 3 distinct categories or classes: Class I and II products which are expressed on the cell surface and Class III which are serum proteins included in the complement system.[5]

FIGURE 1: THE HLA SYSTEM IN CHROMOSOME 6



THE HUMAN HISTOCOMPATIBILITY SYSTEM

Class I Products

Three different antigens are serologically indentified within this class: HLA-A, HLA-B and HLA-C. Class I molecules are glycoproteins. Their basic structure is similar for the 3 types, HLA- A, B and C and consists of 2 polypeptide chains, α and β, and a carbohydrate residue, attached to the external portion of the α chain (Figure 2). The α chains (heavy chains, 44,000 MW) are the gene products of the 3 HLA loci, A, B, C. Each heavy chain has several regions: a short carboxyterminal intracellular portion, a transmembrane segment, and an external aminoterminal region consisting of 3 domains, 1, 2, 3.[5,6] The structure of the genes coding for the Class I α chain of the 3 different antigens HLA A, B, and C is basically similar, consisting of several exons encoding the different domains.[7,8] Polymorphism within each Class I antigen is marked and is mainly given by aminoacid variations in the $\alpha 1$ domains.[6]

The β chain (light chain, 12,000 MW) is the $\beta 2$ microglobulin which is external and noncovalently attached to the α chain. It is nonpolymorphic and is encoded by a gene in chromosome 15; its aminoacid sequence shows some homology with the constant region of the heavy chain of IgG.[9]

Human Class I products are expressed on the cell membrane of all nucleated cells, where they are randomly

distributed as separate antigens. They are serologically detected on lymphocytes using standard known alloantisera obtained from pregnant women and transplant and transfusion recipients. A major problem with this technique is that these sera, although absorbed, are still polyspecific: crossreactivity is occasionally observed as some of the determinants detected may be shared by different antigens within the same group.[6] Also, some of the antigens initially described have been since split in 2 or more new distinct specificities. Monoclonal antibodies are being developed at a fast pace, however, they are still in the experimental phase and are not used for routine typing. As mentioned above, polymorphism within the Class I antigens is marked with more than 20 recognized specificities for the A locus, 40 for the B locus and 8 for the C locus.[10]

The precise function of the Class I products is still unknown. A major role appears to be their participation in lymphocytotoxic reactions. They are the main antigens recognized by cytotoxic T lymphocytes. They also appear to act as cell surface receptors for diverse antigens, in particular viral, that are then recognized and killed by cytotoxic lymphocytes: a cytotoxic T cell cannot lyse a virus-infected cell unless it carries the same Class I antigen (Class I restriction).[11]

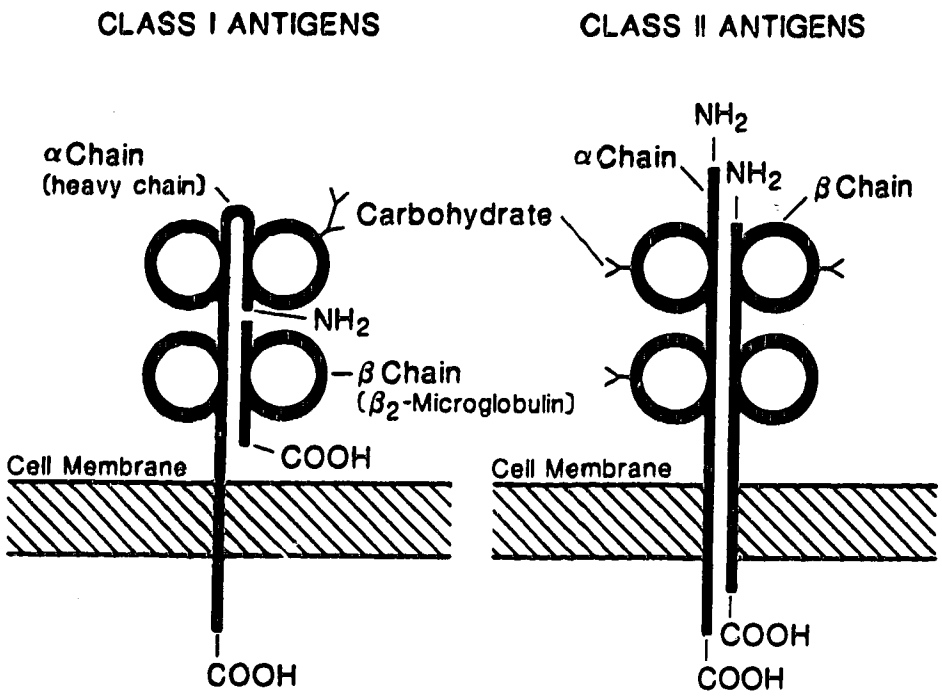


FIGURE 2: THE HLA ANTIGENS: CLASS I AND CLASS II PRODUCTS

Class II Products

Class II antigens are heterodimers consisting of 2 noncovalently associated chains, α(34,000 MW) and β (29,000 MW). Both chains are glycosylated. Each chain has 4 domains: a carboxyterminal intracellular portion, a transmembrane segment, and 2 external domains (Figure 2). Polymorphism is due to variations in the β1 domains and some α1 domains. Three different Class II molecules have been described and they are designated HLA-DP, HLA-DQ and HLA-DR. Each antigen is encoded at a distinct genetic subregion: one (DR) or two (DP, DQ) distinct exons coding for the external domains of the α chains and 2 (DP, DQ) or 3 (DR) for β chains are found in each subregion. Allelic products of each D subregion are combinations of the α and β chains.[6,12]

Class II antigens are only expressed in the cell surface of a few specialized cells that include: B lymphocytes, macrophages, monocytes, dendritic cells and activated T cells. The 3 different antigens, HLA-DP, HLA-DQ and HLA-DR, are defined by different methods that include: serologic typing of B lymphocytes, mixed lymphocyte reaction using known homozygous typing cells, and primed lymphocyte typing. As for Class I antigens, considerable polymorphism is also observed.

The functions of the Class II antigens appear to be multiple: a) there is evidence to suggest that they might represent the human analogue of the murine Ir genes

that control the genetically determined immune response to different antigens;[13] b) they have a major role in antigen presentation to specialized cells: lymphocytes recognize foreign antigens in the context of self, that is, by simultaneously recognizing their own Class II specificities (Class II restriction);[14] c) they are also implicated in cell-cell interactions in the immune system, again by recognition of surface antigens.[15]

Class III Products

Class III molecules are serum proteins of the complement system and include the Bf, C4a, C4b, and C2 factors. Some polymorphism has also been described for this class. The genes coding for Class III products are located between the Class I and II genes.

Basic Genetics of the HLA System

Expression of the HLA alleles is codominant; thus, in each individual 2 sets of HLA antigens, one from each parent, are detected. Each set of linked alleles, or haplotype, is located on a single chromosome 6. Every individual then, possesses 2 distinct HLA haplotypes, maternal and paternal, that can be determined by family studies.[3]

The entire human MHC is situated within a distance of 3-5 cM: recombination between the A and D locus is less than 3% and we can consider the HLA genes as closely

linked. This region is highly polymorphic with several alleles described for each HLA gene: this diversity results in multiple distinct haplotypes that are found in the general population. Epidemiologic studies show particular racial distributions of the different antigens and associated haplotypes. Another striking feature of the HLA system is that the occurrence of particular haplotypes is not random. A phenomenon designed as "linkage disequilibrium" has been described: some alleles tend to occur together more frequently than could be expected by random association; thus, some haplotypes are observed more often than expected by chance. Whether this represents a selection process related to survival advantages is still under discussion.

B. HLA AND DISEASE: GENERAL CONSIDERATIONS

Several diseases have been associated to certain HLA antigens.[16] In some cases the association has been described for a single antigen (as B27 and ankylosing spondylitis)[17,18] and in others it is an entire haplotype that is linked to the disorder under study (i.e. A3B14 and hemochromatosis).[19]

Most disease associations relate to Class II antigens and autoimmune disorders. This has led to the belief that a disturbed immune response to one or more antigens might trigger most of these conditions. Several

other pathogenetic mechanisms have also been postulated, depending on the nature of the association. The major current hypotheses are described below:

1. The linked gene hypothesis: This theory suggests that the MHC genes are not actually involved in the pathogenesis of disease but are closely linked to the responsible gene. This indeed has proved to be true in some cases. Congenital adrenal hyperplasia is a recessive disorder caused by inadequate production of C21-hydroxylase. An association to HLA antigens has been described: this is due, however, to the fact that the HLA system and the responsible gene are both located on chromosone 6 and closely linked.[20]

2. The "molecular mimicry" hypothesis: It has been suggested that some HLA antigens may share determinants with external factors such as bacteria or virus.[21] This would imply some degree of cross reactivity, with the immune responses against the external antigens reacting against self components. The HLA-B27 antigen which is associated with ankylosing spondylitis carries a sequence of 6 amino acids which is also found in a Klebsiella pneumonia protein.[22] Furthermore, cross reactivity between B27 and Klebsiella has been well documented.[23,24]

3. The receptor hypothesis: According to this theory, certain HLA molecules acting as receptors for determined antigens would be modified by the interaction,

elliciting an immune response against self. Host cells would then become susceptible to lysis.[25]

4. The altered immune response hypothesis: As mentioned before, at least some Class II genes are believed to be the human counterparts of the murine Ir genes controlling the immune responses to specific antigens.[13] The presence in the host of a particular HLA-D allele could lead to an increased or abnormal immune response to one or more antigens. The disturbed immune function would then result in the pathogenetic mechanisms responsible for the clinical manifestations observed in many of the so-called autoimmune disorders.[26,27]

The description of several HLA-disease associations has opened an entire new field of research. However, several points remain unclear. In most cases, it is still unknown whether it is the HLA alleles or closely linked genes that are responsible for disease susceptibility. Often, more than one HLA allele is linked to a particular condition which may suggest some degree of linkage disequilibrium with another gene. The HLA association can be marked and constant (like in ankylosing spondylitis) or weak and disclosed only in extensive population studies. Furthermore, in some cases, a particular HLA allele does not seem to increase the risk of acquiring the disease but might modify or alter the clinical expression and/or severity and even

the response to a specific therapy. Individuals with psoriasis and particular HLA antigens such as Cw6 appear to have an earlier onset of disease.[28] Another example are patients with rheumatoid arthritis and HLA DR2 and/or DR3 who appear to be more susceptible to the toxic effects of gold compounds.[29]

In general, with a few exceptions such as the C21-hydroxylase deficiency,[20] the mode of inheritance of these disorders is unclear. Twin and family studies show inconsistent patterns with variable penetrance that suggest a polygenic and/or multifactorial basis. This is particularly true for the rheumatoid diseases under consideration.

C. HLA-B27 AND THE SPONDYLOARTHROPATHIES

The spondyloarthropathies are a group of rheumatic diseases that share several clinical and genetic features. They include ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis and the arthritis associated with the inflammatory bowel diseases.[30] Common features of these disorders are:

- Absence of rheumatoid factors
- Tendency to familial aggregation
- Frequent but variable involvement of the spinal joints (always in ankylosing spondylitis, occasionally in psoriatic arthritis)

- Common pattern of peripheral joint arthritis, usually asymmetric and affecting a few joints
- Occasional extra-articular involvement: inflammation of the eye, heart, skin and mucose membranes
- Association to the Class I HLA antigen B27

The linkage of HLA-B27 to the spondyloarthropathies is well recognized, though variable in frequency for the different disorders. None of the HLA-disease associations has been as marked and well studied as the B27-ankylosing spondylitis relationship.

Ankylosing spondylitis (AS) is a rheumatic disease affecting young adults, particularly men, the male/female ratio being 4:1. It is characterized by an insiduous onset of persistent back pain and stiffness.[31] The symptoms usually begin in the lower back with arthritis of the sacroiliac joints (sacroiliitis) and during the following years may progress to involve the entire spine. Peripheral joints, in particular of the lower limbs, are occasionally affected. Ankylosing spondylitis is diagnosed on the basis of clinical and typical radiological features. Diagnosis, however, might be uncertain if the radiological changes characteristic of the disease are absent: this may account at least for some of the variability seen in the epidemiological and genetic studies on the disease.

Early studies had shown some indication of genetic predisposition to AS;[32] however, it was the discovery of

the strong association of HLA-B27 to spondylitis[17,18] that opened a new field for further research into the pathogenesis of this disease. Epidemiological studies on Caucasian populations show some variability in the prevalence of AS ranging from 0.5 to 4 in 1000.[33] The overall frequency of HLA-B27 in Caucasians with AS is 90%, compared to 8% in the general population: this gives a relative risk of about 100, so far the strongest relative risk observed for an HLA-disease linkage. This association remains constant across most racial groups, the only exception being African and North American Blacks.[34] In this group, only 50% of the patients are B27 positive. North American Indians have a high frequency of B27 and, as expected, the prevalence of AS in this population is strikingly high.[35]

Family studies before HLA typing was available showed a clear familial aggregation,[32] however, the pattern of inheritance was not apparent: there was some indication of the presence of a single or major effect gene with incomplete penetrance, but results were not consistent.[36] Recent family studies with HLA typing have clarified some of the genetic aspects involved. It has been determined that about 20% of the B27 positive relatives of B27 positive AS patients will develop AS;[37] on the contrary, B27 negative relatives are invariably spared.[36] Why only a minority of the B27 positive relatives will develop the disease is still unknown.

Studies on monozygotic twins[38] have shown that indeed the penetrance of AS is incomplete, suggesting a multifactorial etiology that would include environmental factors. Family studies show that the prevalence of AS is significantly higher in B27 positive relatives of AS patients, compared to B27 positive controls and to relatives of B27 positive individuals without AS: the risk of acquiring the disease is not the same for all B27 positive individuals.[36,39-41] Environmental factors such as an infectious agent could be expected to occur more frequently in some families than in others and this again could account for the differences observed. Other genetic factors such as heterogeneity of the B27 antigen or additional genes (HLA or non-HLA linked) have also been suggested as possible explanations.[36] Athough the risk of AS is greater for males, sex-linked inheritance does not occur. This favors a sex-influenced polygenic inheritance. Studies in families with 2 separate and distinct haplotypes have shown that AS tends to occur more frequently in family members sharing only one of the two B27 haplotypes.[42,43] These findings would suggest that the B27 antigen is not the only genetic factor related to the development of AS: as environmental factors such as an infectious agent are expected to have the same effect in all B27 positive individuals within a family. Similarly, if a gene on a chromosome other than 6 were also implicated, the same disease prevalence would

be expected in patients with either B27 haplotype. Two possible explanations for these findings are: 1) B27 is heterogenous or polymorphic, 2) an additional gene or genes implicated in AS are HLA linked.

HLA antigens are serologically defined with polyclonal alloantisera, thus, variation of a particular antigen might be expected as some specificities may be shared while others may be unique for a particular subtype. Heterogeneity of the serologically defined B27 antigen does indeed occur. Several laboratories have succeeded in creating monoclonal antibodies as well as cytotoxic T cell lines which specifically identify several distinct B27 subtypes.[44,45] Studies with monoclonal antibodies tested against a panel of HLA typed donors (B27 positive and B27 negative) have determined that cross-reactivity with other B locus antigens also occurs and that one subtype might react with more than one monoclonal antibody: the different patterns observed appear to indicate that polymorphism of the B27 antigen occurs at more than one epitope.[44] These different variants (at least 6 have been described)[44-48] have varying frequencies according to the ethnic group under study, yet, clinical studies involving AS patients and B27 positive healthy controls have failed to identify a distinct subtype that selectively relates to disease: so far, all subtypes described seem to be equally distributed in patients and controls.[48-50]

If different B27 subtypes do not correlate with AS, additional genes must then be implicated in the pathogenesis. The "two gene theory", based on the linkage disequilibrium observed within the HLA region, has been proposed to explain the B27 link to disease.[36] It suggests that an unidentified gene responsible for AS is in linkage disequilibrium with the B27 gene whose product is then recognized acting as a genetic marker, not specifically involved in the pathogenesis. Ten percent of the patients with AS are B27 negative; although this fact could be considered a source of evidence for the presence of a putative linked gene, B27 negative AS appears to be genetically and clinically distinct from B27 positive AS. Family studies in B27 negative patients show that these cases are sporadic and no familial aggregation is observed.[51] Furthermore, some clinicians believe that B27 negative patients have a milder clinical course, usually limited to the lower spine. Frequently, these patients (or their relatives) have other associated disorders such as psoriasis or inflammatory bowel disease. These features indicate that B27 negative AS patients might be a distinct group within the AS population.[36,51] Several other observations argue against the linked gene theory. The association of AS with B27 occurs in every ethnic population tested so far. If a linked gene and not B27 were responsible for AS, the linkage would have to be extremely strong with no

recombination to explain the persistence of the association in different ethnic groups split thousands of years ago. From our knowledge, this does not appear to be true as recombination between the different HLA loci is occasionally observed (with a frequency of 0.01 to 0.02). For the same reasons, as recombination in the HLA region does indeed occur, it might be expected that occasionally, a family carrying a B27 haplotype would show genetic recombination at the B locus and a B27 negative individual would develop AS. Although this has been reported in a few instances,[52] results have not been consistent and large family studies have been unable to prove this theory.

Present evidence seems to indicate then that B27 itself is involved in the pathogenesis of AS. From the data reported it is clear that if a particular B27 subtype is not specifically related to AS an additional gene or genes, probably HLA linked, must be implicated. The search for other linkages within the MHC region has proved unsuccessful. No association has been found with antigens from the D/DR region.[53] Class I antigen A2 was found in 40% of the B27 haplotypes of AS patients, however, controlled studies showed that this assocation was due to linkage disequilibrium with B27 as the frequency was the same in the B27 positive control population without AS. A recent study, however, has shown an increased prevalence of the B60 antigen on the

non-B27 haplotype in patients with AS. The significance of this is still unknown. Distribution of the Class III (complement) alleles and glyoxylase subtypes, which are also encoded in the vicinity of the HLA region, is also similar in patients and healthy controls.[54]

Restriction fragment length polymorphism (RFLP) analysis has been used by some investigators as an approach to further define the genetic aspects at the DNA level.[44,55,56] One study reported results on 53 patients and 107 controls using a 1400 bp full length B7 probe which is at least 85% homologous with the coding region of the B27 allele.[56] After treatment with selected restriction enzymes and hybridization to Southern blots, a 9.2 kb PVU II fragment was observed in 73% of the B27 positive patients and only 23% of B27 positive controls. Family studies in a few patients showed that the fragment did not always segregate with B27 and was occasionally contained in the other HLA haplotypes. Other groups have been unable to obtain the same results with this fragment.[57] A few other DNA restriction studies have also been reported but they have been performed in limited numbers of patients and results are not conclusive.[44,55]

The role of infection in AS was suggested as early as the 1950's, linking the development of AS to genitourinary infections, in particular prostatitis.[58] These observations and the association of AS to

inflammatory bowel disease led to research in the role of bacteria in the development of AS. An initial study reported cross-reactivity between HLA-B27 and several gram negative bacteria.[59] One of these organisms, Klebsiella pneumonia, could be isolated from the bowel flora of AS patients more frequently than from controls.[60] Rabbit antisera to HLA B27 positive lymphocytes has been shown to be active against Klebsiella pneumonia and monoclonal antibodies against B27 have also reacted with this strain.[23,24] Furthermore, rabbit antisera against Klebsiella pneumoniae exhibited lymphocytotoxic activity against B27 positive lymphocytes.[23] The same group also reported an increase in the IgA antibodies to Klebsiella in the serum of AS patients.[61] These investigators then proposed "a cross tolerance or molecular mimicry hypothesis" suggesting that antibodies against enteric bacteria, in particular Klebsiella, react with self antigens producing a chronic inflammatory disease.[62] A recent report using a computerized search has established that molecular mimicry between Klebsiella pneumoniae and the B27 antigen indeed occurs: a Klebsiella protein, nitrogenase reductase carries a sequence of 6 amino acids homologous to a B27 segment.[22] Cross-reactivity using synthetic peptides carrying this sequence has also been demonstrated. Rabbit antisera against one of the B27

peptides also reacted against the intact B27 cells and the intact Klebsiella protein.

A second theory more difficult to prove has been elaborated by a different group that also reported cross-reactivity between B27 and Klebsiella pneumoniae, however, in this study the lymphocytotoxicity of their sera was usually limited to B27 positive cells of AS patients and seldom occurred with B27 positive cells of healthy controls.[25,63] Subsequently, they determined that culture filtrates from this strain could transiently modify B27 positive lymphocytes of healthy controls in such a way that they became susceptible to lysis by Klebsiella antiserum.[64] This group suggests that B27 positive cells act as a receptor that binds a Klebsiella derived "modifying factor" (a plasmid perhaps)[65] which is then incorporated into the cell. This factor modifies the B27 positive cell which then becomes cross-reactive with Klebsiella. The attraction of this theory lies in the fact that the Class I antigens are known to act as receptors for viral antigens and to regulate T cell cytotoxicity.

Enough evidence has been documented to accept that AS is a multifactorial and probably polygenic disorder with an HLA linked genetic susceptibility and a triggering environmental factor, almost certainly infectious. However, many observations are still unresolved: why AS occurs predominantly in males is

still unknown as no genetic or environmental causes have been found that could explain this difference. Another major question relates to the tissue distribution of AS: if cross-reactivity with a bacterium indeed occurs and causes AS, why would some tissues be more susceptible than others if all nucleated cells express Class I antigens?

Some individuals, otherwise healthy, develop an acute or subacute reactive arthritis in the peripheral joints following an intestinal or venereal infection in the absence of detectable intact microorganisms in the joints.[66] This reactive arthritis, also called Reiter's syndrome, occurs mainly in B27 positive individuals (90%) and also shows familial aggregation. Some of these patients later develop a spinal disease clinically similar to AS. Several bacteria have proved to cause this syndrome and include different strains of Yersinia, Salmonella and Shigella among others.[67] Cross-reactivity between Yersinia enterocolytica and the B27 antigen has also been well documented.[68]

The role of B27 in psoriasis and psoriatic arthritis is more controversial and not as clear as for the above disorders. The relationship of ankylosing spondylitis and B27 to psoriasis will be discussed in detail.

2. PSORIASIS AND PSORIATIC ARTHRITIS

A. PSORIASIS: GENETICS AND PATHOGENESIS

Psoriasis is a common, chronic and relapsing skin disorder present in 1 to 2% of the general population.[69,70] Psoriatic lesions are usually typical; however, the range of clinical variation is considerable, in particular regarding severity and extent. The primary lesions are scaly, erythematose plaques of variable size and shape. Nail involvement (onicodystrophy) is also common. Several varieties have been described and include: psoriasis vulgaris (classic, well defined plaques), guttate psoriasis (small, generalized lesions), pustular psoriasis.[71] All these morphologic patterns, however, share common histologic features and are considered clinical variations of the same disorder. The general lesions are those of an increased cellular proliferation of the epidermis with marked shortening (up to 8 fold) of the epidermal cell cycle.[72,73] Characteristic histologic features include parakeratosis, absence of the granular layer and an inflammatory infiltrate of the upper dermis and epidermis.[74] Microabcesses are also observed. There is increased HLA-DR expression in keratinocytes and mononuclear cells which correlates well with disease activity.[75,76]

The precise etiology of psoriasis is still unknown. However, the role of genetic predisposition has been well established:

1) There is an increased prevalence of psoriasis in relatives of affected individuals as compared to the general population.[77-79]

2) Studies in twins show a high degree of concordance in monozygotic twins.[80-82]

3) An association to some HLA antigens has been described.[83-91]

The pattern of inheritance, however, is not constant and does not follow a precise model of classic autosomal dominance or recessiveness.

Genetics: Twin Studies

Several studies have reported the rates of concordance in monozygotic and dizygotic twin pairs with psoriasis.[80-82] The differences observed confirmed the role of genetic predisposition in the development of psoriasis: approximately 65% of monozygotic twins are concordant for psoriasis as compared to 25% of dizygotic pairs. The fact the concordance in monozygotic twins is not complete (100%) suggests an additional role of environmental factors.

Genetics: Pedigree Analysis

Pedigree analysis has not shown a constant pattern of inheritance. Half of the cases occur in the absence of a positive family history, furthermore, all types of parent-offspring transmission are observed: unaffected parents-affected offspring, affected parent (1)-

affected/unaffected offspring, affected parents (both)-affected/unaffected offspring. The major risk appears to exist when both parents have psoriasis: 50% of the children will develop psoriasis.[79] A major problem in determining a common pattern of inheritance is the fact that psoriasis can virtually develop at any age:[77,78] an unaffected relative may develop the disorder later in life. All of these observations, nevertheless, suggest a polygenic, multifactorial inheritance of psoriais.

Genetics: Association to HLA Antigens

The association of psoriasis to different HLA antigens is well recognized. The HLA types that have been most frequently reported are Class I antigens and include B13, B16, B17, and CW6.[83-91] The strongest assocation is with CW6 which gives a relative risk of developing psoriasis of about 9 or 10.

Systematic studies on the familial segregation of psoriasis in regard to inheritance of the different HLA haplotypes have not been published so far. However, a few reports on selected families appear to show a correlation between the inheritance of HLA haplotypes and the development of psoriasis: probands and affected close relatives appear to share at least 1 HLA haplotype.[92,93]

Etiopathogenesis

As already mentioned, heredity is the best recognized factor affecting the development of psoriasis, yet, the exact mechanism underlying the association of psoriasis to the genetically determined HLA antigens is still unknown. It is generally thought that determined external agents may act in a genetically predisposed host as triggering factors leading to the development of disease. Several trigger factors have been well recognized. Skin injury is known to precipitate or exacerbate psoriasis: the Koebner phenomenon refers to the development of psoriatic lesions after injury of normal skin.[94] Infection, in particular streptococcal, has also been shown to be a trigger factor. Psoriatic flares are often observed after upper respiratory infections, particularly in children.[95] Furthermore, acute guttate psoriasis frequently follows a streptococcal disease.[96,97] How these trigger factors lead to disease in genetically determined individuals is still a matter of speculation. Psoriatic keratinocytes express HLA-DR molecules on their surface which are not seen in normal controls.[75,76] This suggests persistent activation by bacteria or other antigens. Abnormalities in several systems have also been described and include capillary changes,[98] alterations in neutrophil function,[99,100] and biochemical aberrations in the abnormal skin, such as decreased intracellular levels of

cyclic AMP[101] and increased lipoxygenase activity and leucotrienes, which are strong chemotactic factors.[102,103]

B. PSORIATIC ARTHRITIS: GENETICS, PATHOGENESIS AND RELATIONSHIP TO HLA-B27

The association between psoriasis and seronegative arthritis is well recognized. It has been estimated that 1 to 20% of the patients with psoriasis will develop arthritis.[104-107] The female to male ratio is approximately equal[105,108,109] and the onset is usually during the 3rd or 4th decade of life but it can start at any age.[105,109-111] Cutaneous psoriasis precedes the arthritis in most cases but in 10 to 15% of the patients the arthritis develops first.[110,111] Different patterns of arthritis have been described. The most commonly used classification was proposed by Moll and Wright[108] and describes 5 patterns of joint involvement including:

- Asymmetrical oligoarthritis
- Symmetrical polyarthritis
- Distal interphalangeal joint arthritis
- Arthritis mutilans
- Psoriatic spondylitis

Often, patients cannot be ascribed to a single pattern as overlap between the different groups is very common. The most frequent clinical presentation is oligoarthritis:[108] however, during the course of the

disease many patients will develop an asymmetric polyarthritis which is not considered in the previous classification. Some of the forms of arthritis, such as spondylitis and arthritis mutilans, may occur in any of the patterns described above. Furthermore, psoriatic spondylitis is usually associated with peripheral arthritis.[105,112]

The etiology of psoriatic arthritis as for psoriasis is still obscure. Heredity again, seems to be a major factor, yet several observations distinguish psoriatic arthritis from cutaneous psoriasis alone. HLA antigens associated with psoriasis are also present in psoriatic arthritis as expected but a few specificities such as B27 and B38 are only increased in patients with arthritis.[90,109,112-125]

Family studies and pedigree analysis have also shown some genetic heterogeneity. In a large family study, Moll and Wright found an increased prevalence of psoriatic arthritis in relatives of patients with psoriatic arthritis as compared to the general population and relatives of patients with psoriasis alone.[126] Unfortunately, HLA typing was not available at the time of the study. A later publication on 2 families with both psoriasis and psoriatic arthritis appears to show a different HLA haplotype segregation for each disease:[92] relatives with psoriasis alone shared a different haplotype than family members with both psoriasis and

arthritis, suggesting separate genetic influences. Another family case report showed similar results.[93] In both studies, however, several relatives shared the same haplotypes as the psoriatic family members but were disease free. This again points towards a polygenic or multifactorial pattern of heredity.

The pathogenesis of psoriatic arthritis remains unclear. Histologically lesions are similar to those observed in rheumatoid arthritis but of a lesser degree. The main features are hyperplasia of the synovium with variable villous proliferation, thickening of vessel walls and a polymorphonuclear and/or mononuclear cell infiltrate.[109,127] Arthritis often develops after mild trauma to the joint.[128] It is thought that triggering factors such as trauma and infections will cause arthritis in a genetically predisposed individual: whether this is secondary to an immunological or polymorphonuclear cell dysfunction is still unknown. Several abnormalities have been described but often results by different laboratories are contradictory. Normal, increased and decreased responses to mitogens have been reported.[129-132] In general, T cells are reduced in number.[130,132] Low numbers of synovial suppressor cells have also been observed.[133] Many of these abnormalities have been described both in psoriasis and psoriatic arthritis. It would be tempting to assume that psoriatic arthritis may be the consequence of the

persistence of the functional alterations seen in the skin and thus be considered as an extreme form of the disease. A recent report found that patients with extensive DR expression in keratinocytes are more susceptible to develop arthritis.[134] However, the genetic differences between both disorders suggest that at least some additional factors may be present in the development of arthritis. Furthermore, patients with very mild skin disease also develop psoriatic arthritis. A small group of patients develop what has been termed psoriatic arthritis sine psoriasis and they present a pattern of arthritis that is identical to the one observed in psoriasis but with no evidence of skin disease. Often these individuals have a positive family history for psoriasis.

Psoriatic Arthritis, Spondylitis and HLA B27

As already mentioned, some patients with psoriasis develop arthritis of the spine.[108,109,112] Frequently, these patients comply with the proposed New York criteria for the diagnosis of AS,[135] however, in most cases the clinical presentation and course appears to be different from idiopathic AS.[136] Most patients with the so-called psoriatic spondylitis develop arthritis of the peripheral joints. This can also occur in idiopathic AS but to a lesser extent.[137] Furthermore, patients with primary spondylitis seldom have more than 2 or 3 joints involved,

usually large joints in the lower limbs. On the contrary, patients with psoriatic spondylitis often have 5 or 6 joints affected, involving both the upper and lower extremities and commonly the distal interphalangeal joints. Sacroiliitis has been observed in up to 40% of patients with psoriatic arthritis.[105,109,112,123] Very commonly the sacroiliitis is unilateral and asymptomatic as opposed to idiopathic AS where bilateral involvement with significant symptoms is characteristic.[105,136,138,139] Patients with psoriatic arthritis can also develop spinal changes of typical spondylitis, in the absence of radiological sacroiliitis. This is unlikely to be found in AS where sacroiliitis is always the first manifestation of the disease. Furthermore, spinal changes in psoriasis are highly distinctive: syndesmophytes are usually asymmetric and nonmarginal as compared to the fine and symmetric syndesmophytes of idiopathic AS.[136,140]

Epidemiologic differences between both types of spondylitis are also observed. Psoriatic spondylitis is equally distributed between sexes whereas primary AS occurs predominantly in males.[109,111,112] In psoriasis, the age of onset of spinal disease is variable and is not uncommon during the 4th or 5th decade of life. AS seldom occurs after 30 years of age.[141]

HLA-B27 is present in at least 90% of the patients with AS.[30] The other 10% frequently have a history or

family history of associated disorders such as psoriasis or inflammatory bowel disease. Only 50% of the patients with psoriatic spondylitis are B27 positive.[120,141] HLA B27 is also increased in patients with psoriatic arthritis without spinal involvement but in a lesser degree.

All these clinical and genetic differences suggest that spinal involvement due to psoriasis is often, if not always, a distinct disorder from ankylosing spondylitis. Unfortunately, there is no evidence to conclude whether the etiopathogenetic factors described for AS, such as the B27/Klebsiella association, occur in B27 positive patients with psoriatic arthritis and/or axial disease.

3. OBJECTIVES

The two general aims of this study were:

- To define the clinical and genetic characteristics of spinal involvement in psoriasis and psoriatic arthritis.
- To establish the influence of the HLA system in the inheritance of these disorders.

For this purpose we conducted HLA and family studies in selected populations of patients with psoriasis and/or psoriatic arthritis.

1. HLA Study: B27 and Psoriasis

The specific objectives of this study were:

- To determine the prevalence and characteristics of arthritis in a selected population of patients with psoriasis.
- To determine the prevalence of HLA-B27 in this population and its relationship to arthritis.
- To determine the characteristics of spinal involvement in psoriasis and its relationship to HLA-B27.

2. Family Studies

The specific aims of the family studies were:

- To determine whether the inheritance of psoriasis was HLA linked.
- To examine the segregation patterns in families with psoriasis, ankylosing spondylitis and HLA B27 and to determine the relationship and/or linkage between these 3 factors.

CHAPTER 2

HLA STUDY: B27 AND PSORIASIS

1. PATIENTS AND METHODS

Patients were selected from the following sources:

1. PUVA clinics

Unselected, non related patients attending two different PUVA clinics during a given period of time (1986) were contacted. Those who agreed to participate gave written consent and were included in this study. Patients attending the PUVA clinic had a diagnosis of psoriasis by a dermatologist. Most had persistent and/or severe disease requiring chronic therapy.

2. General dermatology clinic

A small number of unselected and consecutive patients attending a dermatology clinic were also included in this study. The main purpose was to include a general population of psoriatics with milder disease.

3. Rheumatic Disease Unit, University of Alberta.

Unselected and consecutive patients with a diagnosis of psoriatic spondyloarthropathy attending the Rheumatic Disease Unit (RDU) at the University of Alberta were included in the study. All patients had cutaneous psoriasis as well.

All patients were seen and examined in regard to peripheral arthritis and spinal involvement. A pelvic x-ray and HLA-B27 typing were performed in all patients. Additional x-rays were performed when required: patients with limitations in the range of motion of the lumbar or cervical spine underwent the standard anterior/posterior and lateral views of these regions. All x-rays were graded by 2 rheumatologists with no knowledge of the clinical or HLA status of the patient.

A. DIAGNOSIS OF CUTANEOUS PSORIASIS

Cutaneous psoriasis was diagnosed following these criteria:

a) Diagnosis by a dermatologist (past or present)

b) Presence of typical psoriatic lesions according to Baker's criteria (Appendix A)[142] confirmed by a rheumatologist of the Rheumatic Disease Unit

Severity was graded according to the extent of the psoriasis.

B. DIAGNOSIS OF PSORIATIC ARTHRITIS

Psoriatic arthritis was diagnosed in the presence of cutaneous psoriasis and one or more of the following criteria:

a) Presence of one or more swollen joints for at least 3 months

b) Radiologic changes compatible with psoriatic arthritis, including erosions in peripheral joints or definite spinal changes (see below)

c) Past diagnosis of psoriatic arthritis by a rheumatologist

C. CLASSIFICATION OF PSORIATIC ARTHRITIS

For the purpose of this study, patients were classified as having:

- Peripheral arthritis: 1 or more of the following joints was involved according to the previous criteria - elbows, wrists, knees, ankles and MCP, PIP, and DIP of the hands and feet.

- Spinal involvement: in the presence of definite radiologic sacroiliitis and/or marked limitation of the lumbar or cervical spine with radiologic syndesmophytes. Radiologic sacroiliitis was graded according to the New York Criteria for the diagnosis of ankylosing spondylitis (Appendix B).[135] A grade II bilateral or III unilateral were required for a definite diagnosis of sacroiliitis.

D. HLA TYPING

HLA-B27 typing was performed at the transplantation laboratory of the University of Alberta, using a microlymphocytotoxicity assay.[5] Standard anti B27 sera from the Canadian Red Cross were used for the typing.

E. STATISTICAL ANALYSIS

Comparisons between groups (means) were analyzed using a two tailed t-test. Proportions were compared using a chi-square (X^2) test or a Fisher's exact test (for values < 6 in one or more cells).

2. RESULTS

A. PATIENTS FROM THE DERMATOLOGY CLINICS: GENERAL CHARACTERISTICS.

Two hundred seventy-six patients (159 males and 117 females) were contacted. One hundred and eighty one patients agreed to participate and were included in the study. Most patients (159) were attending the PUVA clinics and a small proportion (22) had been seen at a general dermatology clinic. No significant differences were observed in age and sex of patients that agreed to participate and patients that were not studied (Table I).

General characteristics of the patients studied are shown in Table II. Patients from the general dermatology clinic were older, had a shorter duration of disease and a later onset. They also had a milder disease, with decreased nail involvement.

No significant differences were observed regarding in particular the different types of arthritis (Table III); 11.6% of the total population of psoriatic patients had psoriatic arthritis, peripheral or axial. Most of these patients had peripheral disease and axial involvement was observed in only 4 patients (2.2%), all with variable degrees of sacroiliitis according to the New York criteria. Three of these patients also had peripheral arthritis; thus, exclusive axial involvement was only observed in 1. This patient was B27 positive.

TABLE I: DERMATOLOGIC PATIENTS: COMPARISON BETWEEN PATIENTS INCLUDED IN THE STUDY AND PATIENTS NOT INCLUDED

	PUVA Pts	Other Derm Pts	Total
No. Contacted	244	32	276
No. Included	159 (65.2%)	22 (68.7%)	181 (65.6%)
No. Male Pts			
Included	95 (59.7%)	12 (54.5%)	107 (59.1%)
Not Included	46 (54.1%)	6 (60%)	52 (54.8%)
Age (Mean±SD)			
Included	44.5±13.1	54.0±14.8	45.6±13.6
Not Included	44.2±13.3	46.1±16.6	44.4±13.7

TABLE II: CHARACTERISTICS OF PSORIATIC PATIENTS ATTENDING THE DERMATOLOGY CLINICS

	PUVA Pts		Other Derm Pts	Total
Total No.	159		22	181
Sex: Male	95 (59.7%)		12 (54.5%)	107 (59.1%)
Age, yrs (Mean±SD)	45.5±13.1	*	54.0±14.8	45.6±13.6
Duration Psoriasis yrs (Mean±SD)	19.0±12.9	*	10.4±8.9	18.0±12.8
Age Onset, yrs (Mean±SD)	25.5±13.6	**	43.6±16.3	27.6±15.1
Severity:				
Mild	49 (30.8%)		15 (68.2%)	64 (35.4%)
Moderate	55 (34.6%)	***	6 (27.3%)	61 (33.7%)
Severe	55 (34.6%)		1 (4.5%)	56 (30.9%)
Nail Involvement	103 (64.8%)	*	7 (31.8%)	110 (60.1%)

* $p < 0.01$
** $p < 0.00001$
*** $p = 0.001$

TABLE III: PSORIATIC ARTHRITIS IN THE DERMATOLOGY PATIENTS

	PUVA Pts	Other Derm Pts	Total
Total No.	159	22	181
Psoriatic Arthritis (Peripheral and/or Axial)	19 (11.9%)	2 (9.1%)	21 (11.6%)
Peripheral Arthritis	18 (11.3%)	2 (9.1%)	20 (11%)
Axial Involvement (± Peripheral Arthritis)	4 (2.5%)	0 (0%)	4 (2.2%)
Exclusive Axial Involvement	1 (0.6%)	0 (0%)	1 (0.5%)
HLA B27	21 (13.2%)	1 (4.5%)	22 (12.2%)

B. PATIENTS FROM THE RHEUMATIC DISEASE UNIT: GENERAL CHARACTERISTICS

Fifty-four consecutive patients were included in the study. All complied with inclusion criteria outlined in section 1 (Patients and Methods). General characteristics of this population are shown in Table IV. Fifty-one patients had peripheral arthritis according to the criteria in section 1C; six of these had spine involvement. The remaining 3 patients had axial involvement with no clinical evidence of arthritis in the peripheral joints. Seventeen (31.5%) were B27 positive.

C. SPINAL INVOLVEMENT

Patients from the 3 different sources (PUVA clinics, general dermatology clinic and Rheumatic Disease Unit) were pooled together to analyze the frequency and characteristics of the spinal involvement and its relationship to the presence of peripheral arthritis and the HLA B27 status.

There was a total of 235 patients included in the study (Table V). Seventy-five had arthritis: 71 (95%) had peripheral arthritis and 4 (5%) had axial arthritis exclusively; 13 of the 75 patients (17.3%) had spinal arthritis. HLA-B27 was positive in 39 patients: 20/75 with psoriatic arthritis (26.7%) and 19/160 without arthritis (11.9%) ($p < 0.05$).

TABLE IV: CHARACTERISTICS OF PATIENTS WITH PSORIATIC ARTHRITIS ATTENDING THE RHEUMATIC DISEASE UNIT (RDU)

Total No.	54
Sex: Male	34 (63%)
Female	20 (37%)
Age, yrs (Mean ± SD)	43.1±12.1
Duration Psoriasis, yrs (Mean ± SD)	15.8±12.3
Duration Arthritis, yrs (Mean ± SD)	8.8±8.4
Nail Involvement	33 (17.8%)
Peripheral Arthritis	51 (94.4%)
Axial Involvement (± Peripheral Arthritis)	9 (16.7%)
Exclusive Axial Involvement	3 (5.6%)
HLA B27	17 (31.5%)

TABLE V: PSORIATIC ARTHRITIS AND SPINAL INVOLVEMENT IN ALL 235 PATIENTS ANALYZED TOGETHER

Total No.	235
Arthritis (Peripheral and/or axial)	75
Peripheral Arthritis	71
Axial Involvement (± Peripheral Arthritis)	13
Exclusive Axial Involvement	4
HLA B27	39

The relationship of axial involvement to the presence of peripheral arthritis and the HLA B27 status is shown in Table VI.

Spinal arthritis was observed mainly in the group of patients with both HLA B27 and peripheral arthritis (23.5%). Both the presence of HLA B27 and/or peripheral arthritis were associated with an increase in axial involvement. Four out of 9 patients with peripheral arthritis and sacroiliitis and 13 of 62 with peripheral arthritis alone were B27+: this difference was not statistically significant. Patients lacking both B27 and peripheral arthritis seldom developed spinal involvement (0.7%).

Seven of the 13 patients with axial arthritis had definite AS according to the New York criteria. Twelve of them had sacroiliitis. The remaining patient showed typical radiological syndesmophytes in the lumbar spine and had marked restriction of the lumbar range of motion. Four patients showed asymmetrical sacroiliitis (Table VII): all of them had peripheral arthritis with mild or absent low back symptoms. Two of them were female. All 3 B27 positive patients without peripheral arthritis and with spinal disease were male and they all had bilateral sacroiliitis.

TABLE VI: RELATIONSHIP OF AXIAL INVOLVEMENT TO PERIPHERAL ARTHRITIS AND HLA B27 (RESULTS ARE EXPRESSED AS NUMBER OF PATIENTS WITH AXIAL INVOLVEMENT/TOTAL NUMBER OF PATIENTS IN EACH GROUP)

	Periph. Arthritis	No. Periph. Arthritis	Total
B27+	4/17 (23.5%)*	3/22 (13.6%)+	7/39 (17.9%)**
B27-	5/54 (9.3%)++	1/142 (0.7%)*++	6/196 (3.1%)**
Total	9/71 (12.7%)#	4/164 (2.4%)#	13/235 (5.5%)

*, ** $p < 0.001$
+, ++ $p < 0.05$
# $p < 0.01$

TABLE VII: SACROILIITIS IN PATIENTS WITH AXIAL INVOLVEMENT

	Total No.Pts.	Axial Arth.(%) (Males)	SI	Asym. SI
Per Ar B27+	17	4 (23.5%) (3)	4	2
Per Ar B27-	54	5 (9.3%) (4)	5	2
No Per Ar B27+	22	3 (13.6%) (3)	3	0
No Per Ar B27-	142	1 (0.7%) (1)	0	0
Total	235	13 (5.5%) (11)	12	4

Per Ar: Peripheral Arthritis

SI: Sacroiliitis

Asym SI: Asymmetric Sacroiliitis

3. ASSUMPTIONS AND LIMITATIONS

Selection of patients in this arm of the study was related to therapy, and thus severity (dermatology clinics), and to the presence of arthritis (RDU). This selection process can bias the epidemiologic characteristics of psoriasis, as severity and arthritis may be related to factors such as age, sex and clinical features. However, the main purpose of this study was to establish the relationship between psoriatic arthritis, HLA B27 and spinal involvement. For this purpose patients were obtained from different sources and pooled together. We are aware of the limitations of this selection method; it is clear that our group of patients does not represent an unselected population of psoriatics. Results and conclusions are thus related to differences between groups of patients, in particular those with and without arthritis.

4. DISCUSSION

One hundred and eighty-one patients with psoriasis attending dermatology clinics were included in the study. Most of them were receiving PUVA therapy and, as expected, had a more severe disease with a longer duration of disease than patients not receiving the same therapy. They also had an earlier onset of disease and a higher frequency of nail involvement which are usually

associated with increased severity.[77,143] Nearly 12% of these dermatology patients had psoriatic arthritis. This is similar to frequencies observed in previous reports.[104-107] We found radiological sacroiliitis in 2.2% of the dermatology patients which is a lower frequency than those reported previously.[105,144] We believe this discrepancy is due to the fact that in other studies x-rays were not read in a blind fashion. This increases the risk of "over finding" pathological results. Our x-rays were rated by 2 different physicians with no knowledge of the clinical or HLA status of patients. Furthermore, x-rays of known AS patients were also included in the reading in a blinded fashion.

Patients from the Rheumatic Disease Unit were included in the study pooled with dermatology patients for two different reasons: 1) to increase the number of patients with psoriatic arthritis and 2) to include patients that otherwise would have been missed. Patients with moderate to severe arthritis frequently receive drug therapy such as methotrexate that may improve the skin condition.[145] These patients often are followed by the rheumatologist and do not attend regularly the dermatology clinic.

When all patients were analyzed together several observations were noted: there was an increase in HLA B27 in patients with psoriatic arthritis compared to patients with psoriasis alone and also to the general

population where B27 is observed in a frequency of about 8%. This has also been generally recognized although a few studies failed to find an association.

Spinal involvement was analyzed in relationship to HLA-B27 and the presence of peripheral arthritis. Both B27 and peripheral arthritis appear to act as separate risk factors for the development of axial disease. B27 positive psoriatics had an increase in spinal arthritis regardless of the presence of peripheral arthritis. Similarly, both B27 positive and B27 negative patients with peripheral joint involvement had an increased risk of axial arthritis. Psoriatics with both peripheral arthritis and B27 antigen had the highest risk: numbers, however, were too small to detect statistically significant differences between patients with one and both risk factors. This leaves the question as to whether B27 and peripheral arthritis may act as additive factors as well: larger number of patients would be necessary to prove this point. We found an increase in the frequency of B27 in patients with peripheral arthritis with and without sacroiliitis. Although this increase was greater in patients with both peripheral and axial involvement, the difference was not statistically significant. A few other studies found this increase to be associated mainly with spinal disease.[124,125] Only one patient lacking both B27 and peripheral disease developed spinal disease. This was a 46 year-old male

with a 24 year history of psoriasis who had severe restriction of the range of motion of the lumbar spine with typical spondylitic symptoms and no evidence of peripheral arthritis. His x-rays, however, showed normal sacroiliac joints but typical non-marginal syndesmophytes as described in psoriatic patients. This has previously been reported in psoriatic arthritis and is very unlikely to occur in primary AS where, as mentioned before, sacroiliitis is always present. Thus, we can still conclude that B27 negative patients without peripheral arthritis very seldom will develop arthritis of the spine.

Interestingly enough, some patients with peripheral arthritis had asymmetric sacroiliitis which is also described as characteristic of psoriatic spondylitis.[138,139] On the contrary, all 3 B27 positive patients with sacroiliitis and no peripheral joint disease had typical spondylitis indistinguishable from primary AS.

This leads us to believe that 2 different forms of spinal arthritis are seen in patients with psoriasis:

1. B27 positive patients without peripheral arthritis develop a spinal disease similar to idiopathic ankylosing spondylitis with bilateral sacroiliitis. This type of involvement was found in a very low frequency. If we consider the patients from the dermatology clinic who are "unselected" at least in relation to the presence

of arthritis, only 1 out of 181 had this type of spondylitis. Nineteen dermatologic patients were B27 positive and did not have peripheral arthritis: this gives a frequency of about 5% of B27 positive psoriatics without peripheral arthritis developing AS. This is within the range of the reported frequencies of AS in surveys of healthy B27 positive individuals (blood donors and population studies).[39,41,146]

It is our impression that in these patients the occurrence of psoriasis and AS is coincidental and both conditions represent here separate disorders. It would be interesting to establish if the same etiopathogenic mechanisms that are described in primary AS, such as the Klebsiella B27 association, are present in these patient.

2. The second group comprises patients with characteristic psoriatic arthritis (either B27 positive or negative) who develop sacroiliitis and spinal disease, usually asymmetric and often asymptomatic, as part of the general clinical picture of arthritis. In these patients, the increase in the frequency of B27 would be primarily due to the association of this antigen to psoriatic arthritis. It could also be possible that B27 had some additional positive effect on the development of spinal arthritis. We found an increased risk for patients with both peripheral disease and B27 but the numbers were too small to reach statistical significance.

Unfortunately, very little has been done in the field of molecular genetic research in these patients. The association of psoriasis to several different HLA antigens makes the choice of an adequate probe somehow difficult. It is interesting to note, however, that in a recent study that found an RFLP-AS association, patients with psoriatic spondylitis, did not have the same related fragment.[56] This report, however, has lately been under discussion as other investigators have been unable to find the same AS association.[57]

Any study on psoriatic spondylitis should very carefully describe the clinical and HLA characteristics of the patients. Up to now, patients have been considered under the same condition. We believe, however, that those who may represent an idiopathic form of AS should be analyzed separately from typical psoriatic arthritis patients.

In conclusion, HLA B27 and peripheral arthritis act as separate factors that increase the risk of spinal arthritis in patients with psoriasis. Patients lacking both only infrequently develop axial disease. The effect of B27 on psoriasis appears to be detected in 2 different ways: as a coincidental factor increasing the risk of idiopathic AS (as for the general population) or as one of the multiple HLA associations that increase the risk of psoriatic arthritis; in this latter case the spinal

involvement would occur as another manifestation of the clinical course of the disease.

CHAPTER 3

FAMILY STUDIES

1. PATIENTS AND METHODS

Two different types of families were selected for this study:

1. Sibship study: HLA haplotype sharing was studied in families with 2 or more siblings with psoriasis. Only families within a reasonable distance from Edmonton were included in the study (usually residents of Alberta). A family history was obtained from the proband; families with a history of psoriasis in both the paternal and maternal sides were excluded to avoid multiplicity of genetic influences. All siblings with psoriasis that agreed to participate in the study either were seen or answered a form questionnaire (when residing outside the Edmonton area). When possible, other first degree relatives were also included. Diagnosis of cutaneous psoriasis was performed according to the same criteria outlined in Chapter 2 (Patients and Methods). HLA-A, B, and C typing was performed in all patients and relatives included.

2. B27 positive family study: the purpose of this study was to analyze the segregation of B27 and psoriasis in families with both traits and to determine their linkage. A few selected families with a history of psoriasis, arthritis or ankylosing spondylitis and a positive HLA-B27 were included in the study. Probands

were selected from the population of patients with psoriasis or psoriatic arthritis included in the previous study (Chapter 2) or from the population of patients with ankylosing spondylitis seen at the Rheumatic Disease Unit in Edmonton during the same period of time. A careful family history was obtained from the proband: families with the traits outlined above were included in the study. In general, the proband was the B27 positive individual as information on the HLA status of other relative was not available at the time of questioning the proband. All probands were seen and examined, relatives were either examined or answered a questionnaire (when outside the Edmonton area). All individuals had a pelvic x-ray to view the sacroiliac joints and HLA-A, B, and C typing. Additional x-rays were taken as required. Psoriasis, psoriatic arthritis and ankylosing spondylitis were diagnosed as outlined in Chapter 2.

HLA typing for the A, B and C antigens was performed at the transplantation laboratory of the University of Alberta using a microlymphocytotoxicity test and Canadian Red Cross antisera.

2. SIBSHIP STUDY

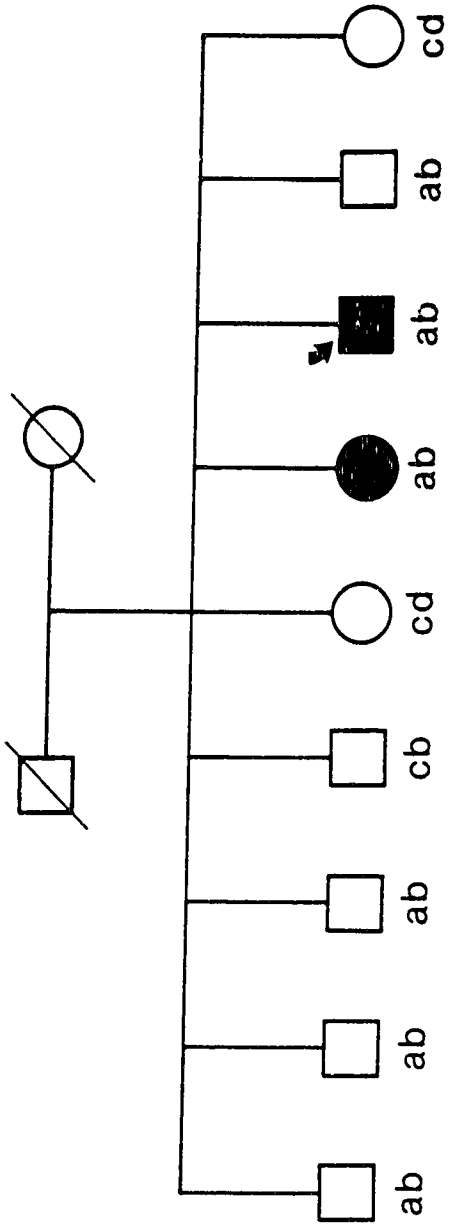
A. RESULTS

Twelve sibships were analyzed (Figure 3-14). Extended family studies including most of the siblings

were performed in 11 families. In family 4 (Figure 6) only 2 sisters with psoriasis were typed, thus, complete HLA but not haplotypes were available; however, both sisters were HLA identical and were assumed to be haplotype identical as well. Families 1, 2, 4, 6, 7, 9, 10, 11 and 12 had each 2 siblings with psoriasis that were available for the study. In family 5 the proband, his identical twin and another brother had psoriasis: only the proband and the non-twin sibling were included in the analysis. Family 8 (Figure 10) had 3 psoriatic siblings and family 3 (Figure 5) had 4: all of them were studied. Thus, 27 siblings (12 male and 15 female) with psoriasis were included. Analysis was performed by comparing observed and expected frequency of haplotpye sharing in the sib pairs. In families 3 and 8, where more than 2 siblings were affected, the proband was paired with each one of the other affected siblings:[147] 3 sib pairs were considered in family 3 and 2 in family 8.

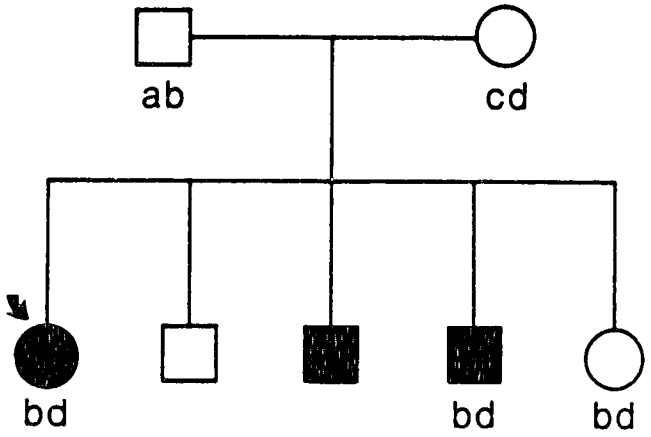
Haplotype sharing was thus analyzed in 15 sib pairs (Table VIII). Expected frequencies of haplotype sharing were estimated as 25% for HLA identity and 50% for haplo identity (only one haplotype). All sib pairs shared at least 1 haplotype and 13 of the 15 were HLA identical compared to the expected frequency of 4 ($p < 0.01$, Fisher's exact test).

FIGURE 3: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 1



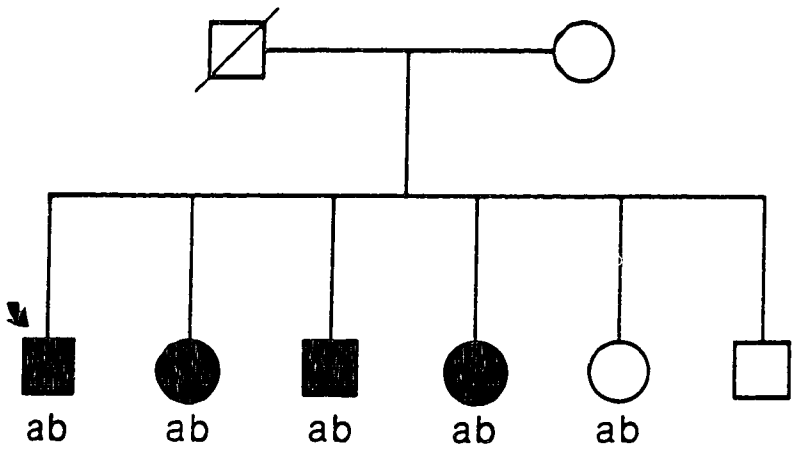
a: A2 B52
b: A32 B35
c: A25 B57
d: A2 B14

FIGURE 4: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 2



a: A24 B15 (HVB)
b: A30 B13
c: A2 B44
d: A2 B62

FIGURE 5: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 3



a: A2 B57
b: A1 B51

(JH)

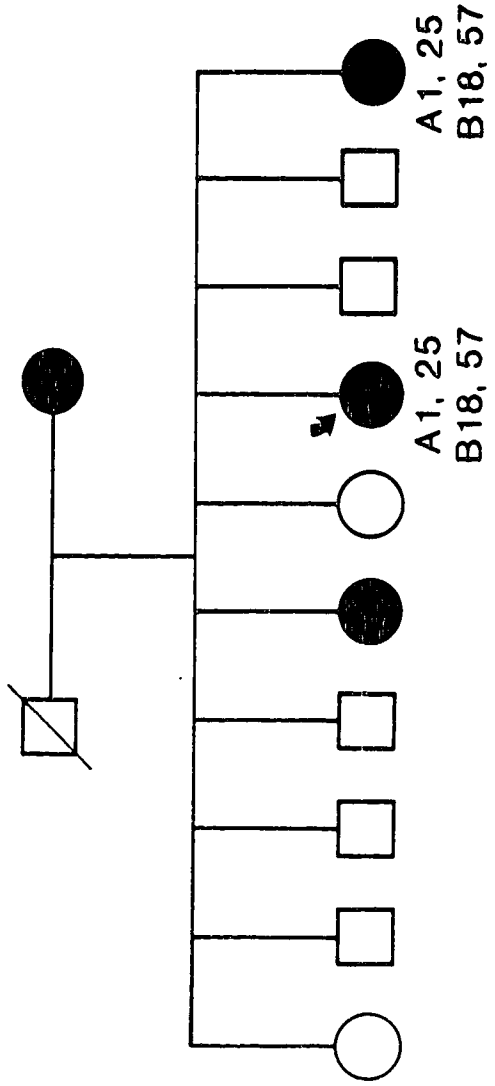
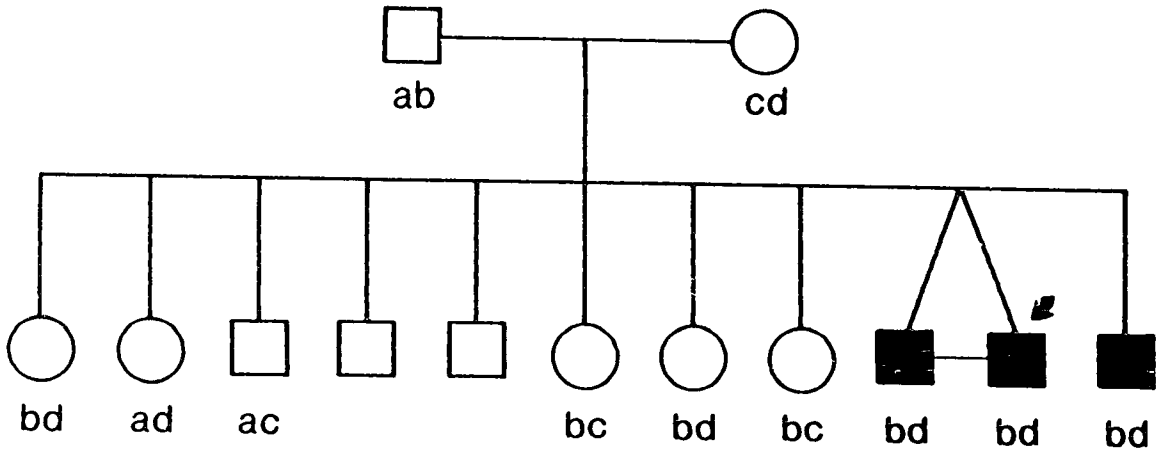


FIGURE 6: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 4

(TS)

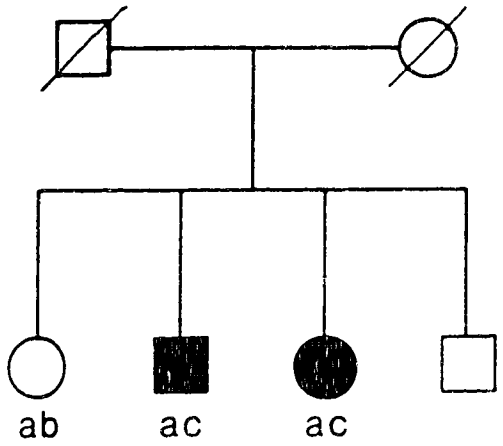
FIGURE 7: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 5



a: A3 B7
b: A2 B35
c: A28 B35
d: A32 B18

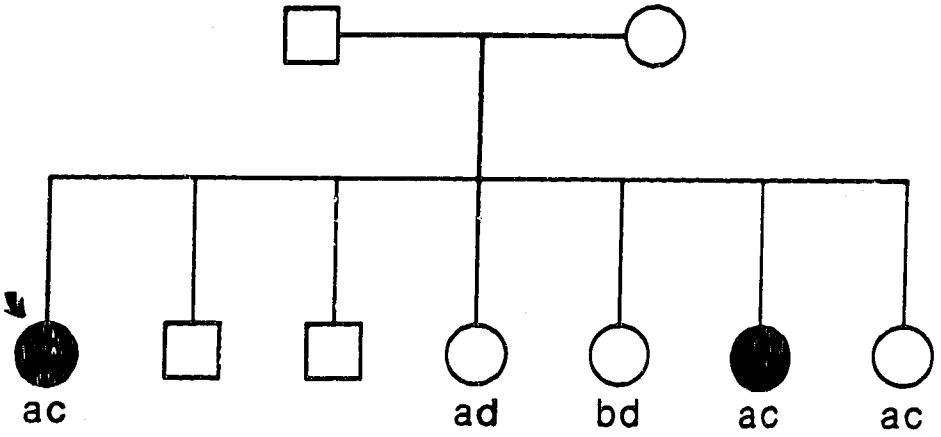
(MA)

FIGURE 8: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 6



a: A2 B57 (AZ)
b: A2 B53
c: A3 B7

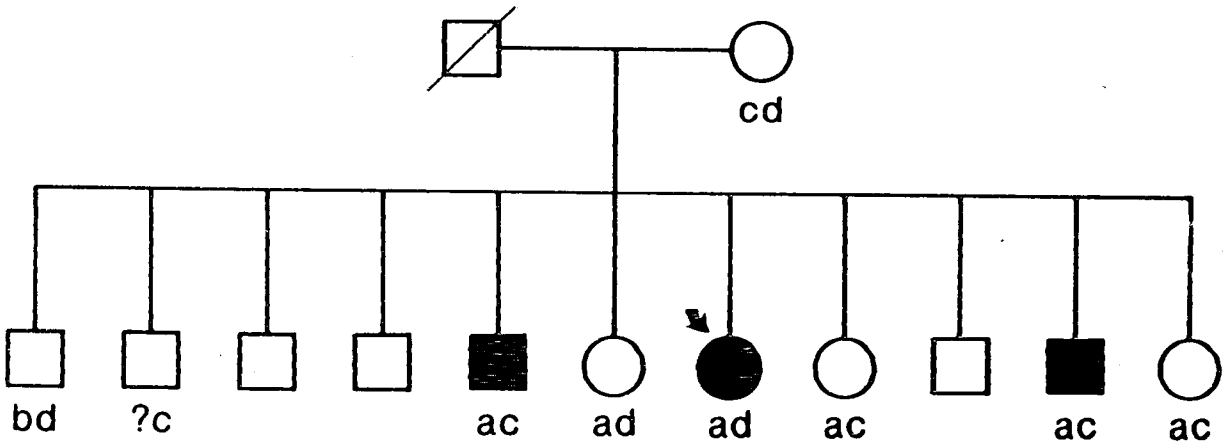
FIGURE 9: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 7



a: A26 B14
b: A3 B7
c: A33 B50
d: A1 B49

(MG)

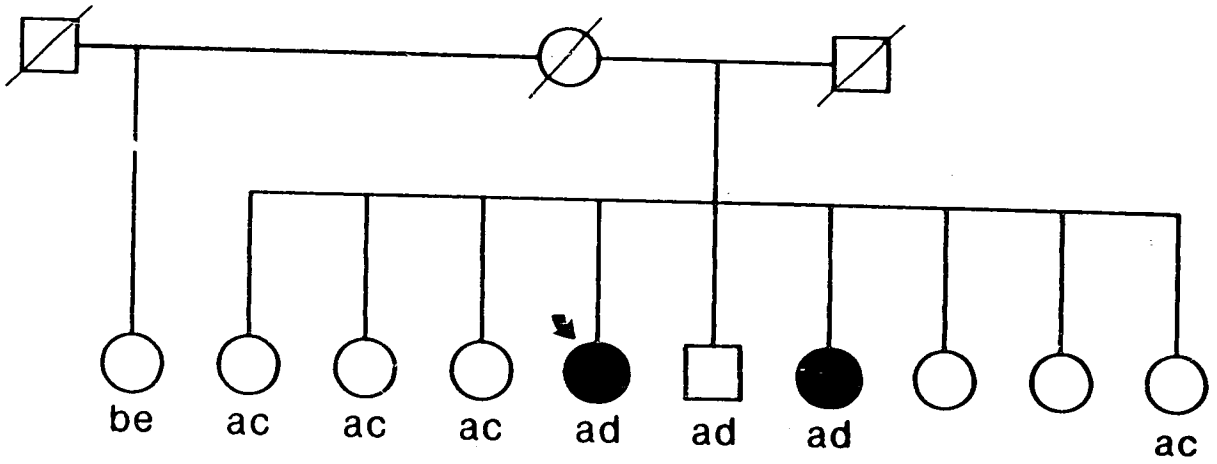
FIGURE 10: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 8



a: A1 B57
b: A2 B52
c: A2 B51
d: A3 B7

(MK)

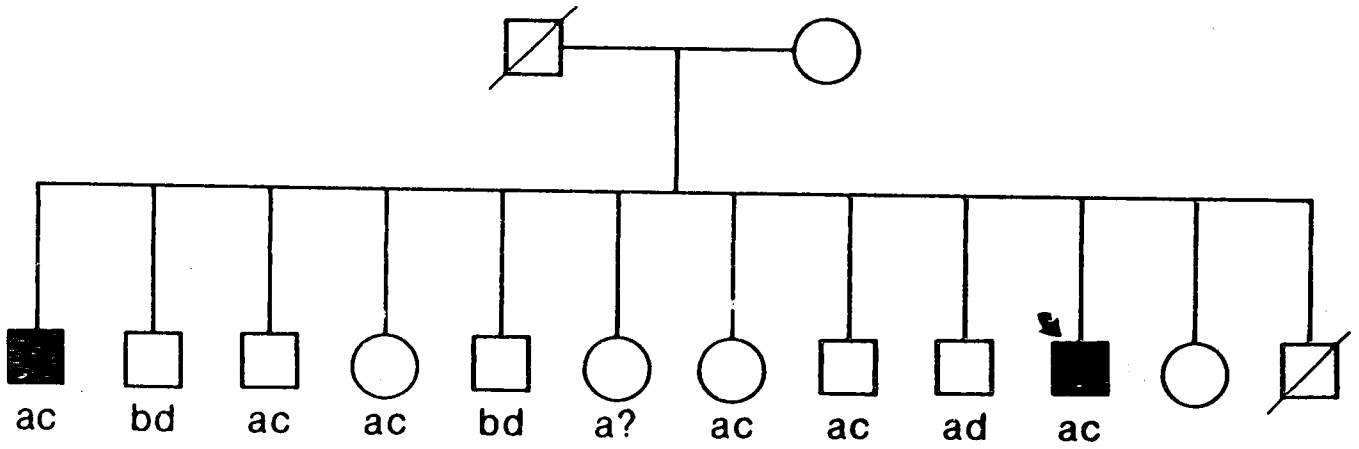
FIGURE 11: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 9



a: A28 B44
c: A32 B35
d: A1 B18
b,e: A24,25 B55,60

(MB)

FIGURE 12: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 10

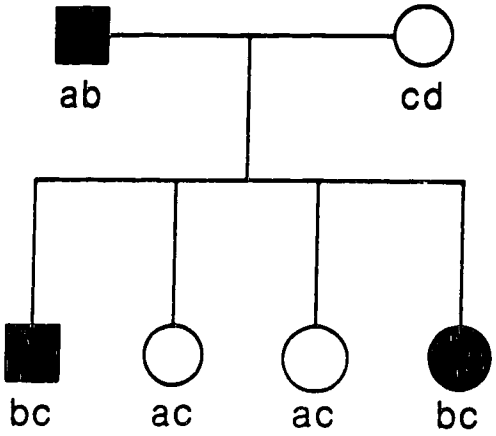


a: A2 B18
b: A31 B35
c: A29 B27
d: A24 B35

(WD)

FIGURE 13: SIBSHIP STUDY IN PSORIASIS.

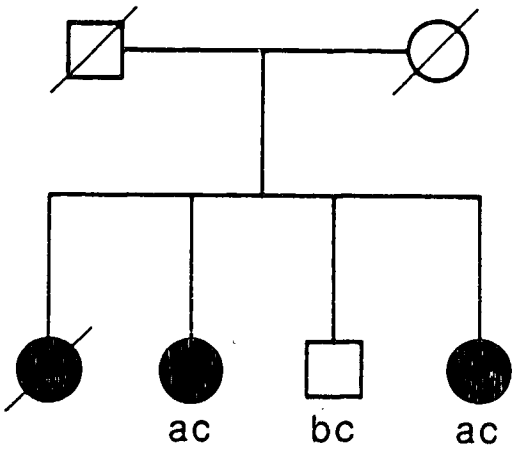
SIBSHIP 11



a: A3 B27
b: A24 B37
c: A26 B44
d: A33 B44

(RF)

FIGURE 14: SIBSHIP STUDY IN PSORIASIS. SIBSHIP 12



a: A2 B27 (SH)
b: A2 B12
c: A3 B57
d: ?

TABLE VIII: HAPLOTYPE SHARING IN SIB PAIRS WITH PSORIASIS

Sib Pairs	HLA Identical	Haplo-Identical	HLA Different	Total
Observed	13*	2	0	15
Expected	4*	7	4	15

* $p < 0.01$

B. DISCUSSION

The role of heredity in psoriasis is well recognized. Yet, the genetics of this disorder appears to be complex and is still unclear. Familial aggregation has been reported in frequencies varying from about 6 to 50%.[148] This discrepancy is also related to differences between the methods employed which vary from simple questionnaires to the proband to physical examination of all relatives of psoriatic patients. All the evidence suggests a polygenic mode of inheritance. Only a few factors have been related to increased transmission and include: concomitant paternal and maternal psoriasis[79] which may be expected, and early age of onset.[78,149] Twin studies have shown that concordance rates are greater in monozygotic twins as compared to dizygotic pairs.[81,82] This concordance is about 60% which indicates a multifactorial inheritance with both genetic and environmental factors implied in the pathogenesis of the disease.

The HLA antigens associated with psoriasis have been the first and only genetic markers to be reported in this disorder. This relationship has been established in epidemiologic surveys of patients with psoriasis and/or psoriatic arthritis but there is a lack of information on the relationship of these antigens to the inheritance of psoriasis in a given family.

The purpose of this study was to determine if there was a particular association between the inheritance of psoriasis and a given HLA haplotype in families. It is clear that our study has different types of ascertainment bias. Families were selected according to different factors that include: 1) knowledge by the proband of family status: families were selected according to family history obtained from the proband; 2) number of family members with psoriasis: only families with at least 2 psoriatic siblings were included; 3) area of residence of family members: only families residing close to the University of Alberta (usually within the province) were included in the study. This selection process may have some unknown effect on the results of our study. The main purpose of the research, however, was to correlate the HLA haplotypes within a family to the development of psoriasis. The HLA status was evidently unknown to the proband at the time of selection, thus, we do not believe that any of the above factors would have any effect on the HLA haplotype sharing in the selected families.

We used a sib pair analysis comparing the HLA haplotypes in affected siblings of these families. All siblings with psoriasis shared at least one haplotype with the proband which suggests the association between the development of psoriasis and the inheritance of a particular haplotype within each family. We expected

this result as it was only logical that the HLA association shown in epidemiologic surveys would determine a linkage between the inheritance of disease and the genetic marker, in this case, a particular HLA haplotype. Yet, most sib pairs shared not only 1 haplotype but were HLA identical. A statistically significant difference was observed when comparing the observed frequencies to the expected rates of HLA identity. We can assume however, that if only one haplotype were related to psoriasis, half of the sib pairs would be haploidentical and the other half HLA identical. Yet, in this case, the binomial probability of 13 or more HLA identical pairs occurring by chance would be very small (< 0.005). The only 2 family studies to our knowledge reporting HLA typing and segregation of psoriasis in a few families also showed an increased frequency of HLA identity in siblings with the disease.[92,93]

These results suggest that more than one HLA linked gene is implicated in the development of psoriasis. If the susceptibility genes were located in a trans position, HLA identity would be detected in siblings carrying the disorder. On the contrary, if both genes were located in a cis position, only one haplotype would be linked to psoriasis; however, still 50% of these siblings sharing this haplotype would be HLA identical. Thus, we can estimate that in a sib study roughly about

75% of the affected pairs would be HLA identical. In cases where the genes were in trans position, each parent would have only 1 of the related genes and thus would not develop psoriasis, however, psoriasis is a very common trait present in 1 to 2% of the population and thus, both homozygosity and/or concomitant presence of the 2 or more involved genes would be relatively common. In families with HLA identical siblings with psoriasis, occasional parents would then have psoriasis. On the other hand, if the genes were inherited in cis position parents would have psoriasis and siblings would be HLA identical in only half of the cases. These figures are compatible with the results we have obtained and would explain some of the variability observed in the inheritance of psoriasis. In addition, we also found that several HLA identical siblings did not develop disease. Although psoriasis can appear at any age, including the last decades of life, it is likely that the observed incomplete penetrance is multifactorial in nature, and includes the effect of presently unknown environmental factors.

Whether the HLA system is directly implicated in the development of psoriasis is still unknown. The multiple non cross reactive HLA antigens associated with the disorder suggest a linked gene as responsible. Yet, the particular nature of the HLA functions and its relationship to antigen recognition and to the immune

system would indicate that the responsible genes are linked to the system, not only geographically but functionally as well.

Future research into the genetics of psoriasis should combine family studies with more extensive basic research. Segregation analysis with HLA typing of both families with a strong familial aggregation and families where only the proband has psoriasis should establish if the proposed patterns of inheritance really occur. Molecular genetic analysis of selected families with adequate HLA probes would also help to define the precise segregation of this disease.

3. B27 FAMILY STUDY

A. RESULTS

Five families were included in this section of the study. All of them had at least 1 B27 haplotype and family members with psoriasis and/or ankylosing spondylitis. All family members were assessed without knowledge of the B27 status. Figures 15 to 19 show the extended pedigrees in these families. Haplotypes are only shown when relevant. Families 1 to 3 were also included in the sibship study.

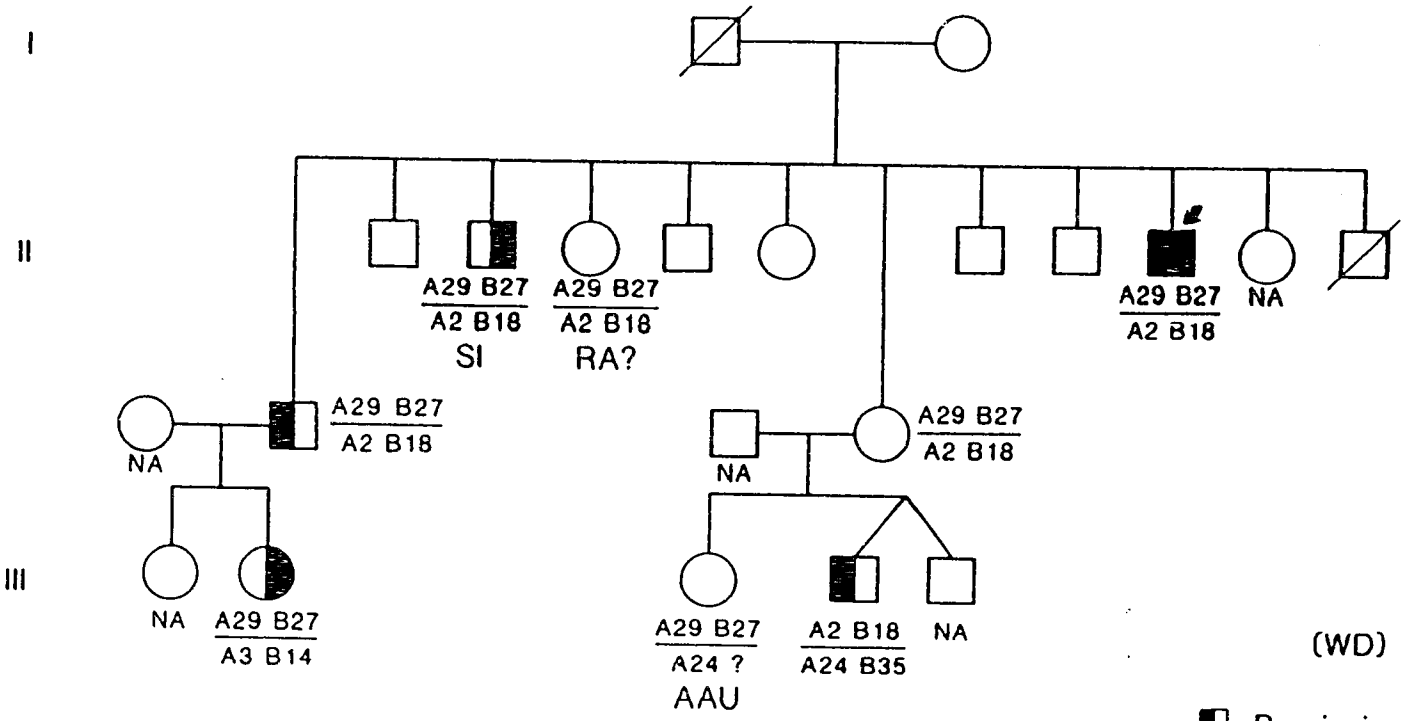
Family 1 (Figure 15)

The proband (II:10) is a 47 year-old B27 positive male with psoriasis, peripheral arthritis and definite AS. Two HLA identical brothers (II:1, II:3) have developed one AS and the other psoriasis. This last sibling with psoriasis has a 46 year-old daughter (III:2) who has inherited the B27 haplotype and has typical AS with no evidence of psoriasis or peripheral arthritis, compatible with psoriatic arthritis. II:7 is one of the proband's HLA identical sisters who does not have psoriasis or AS; however, her 31 year-old daughter (III:3) has inherited the B27 haplotype and has developed acute anterior uveitis, a B27/AS associated condition. One of her twin sons, III:4, has inherited the non-B27 haplotype: he has cutaneous psoriasis.

Family 2 (Figure 16)

The proband is a 16 year-old B27 positive male diagnosed as having juvenile ankylosing spondylitis. His grandfather (I:1) is a B27 positive psoriatic: 2 of his children (II:1, II:4) inherited the non-B27 haplotype and developed psoriasis. His daughter (II:3), the proband's mother, inherited the B27 haplotype and does not have psoriasis.

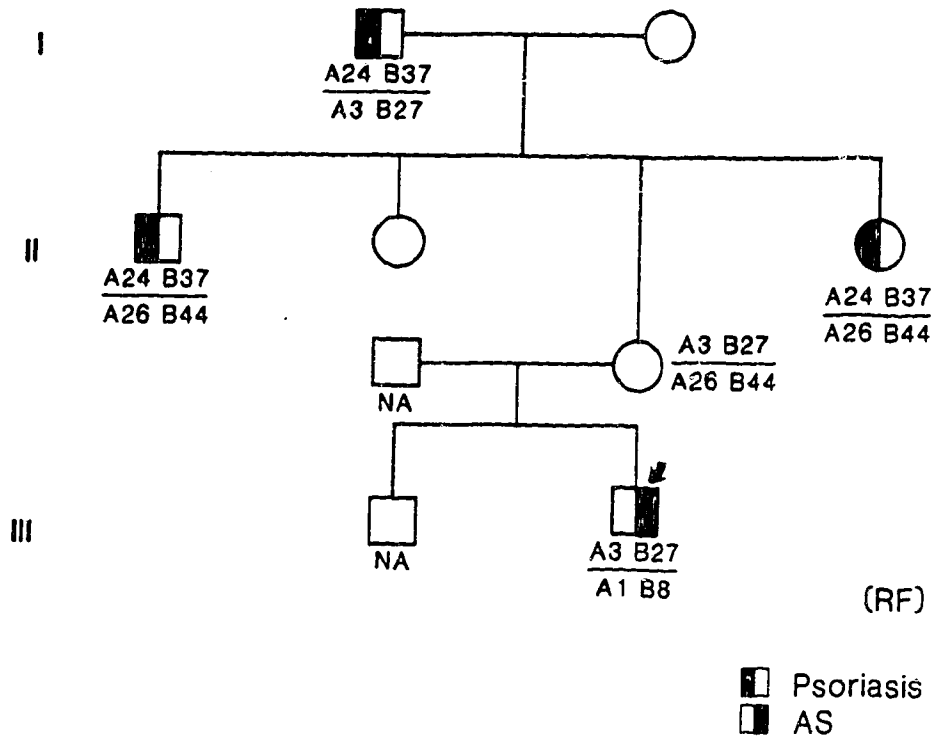
FIGURE 15: PSORIASIS, AS AND B27 FAMILY STUDY. PEDIGREE 1



AS: Ankylosing Spondylitis
SI: Sacroiliitis
AAU: Acute Anterior Uveitis

RA: Rheumatoid Arthritis
NA: Not Available

FIGURE 16: PSORIASIS, AS AND B27 FAMILTY STUDY. PEDIGREE 2



AS: Ankylosing Spondylitis
NA: Not Available

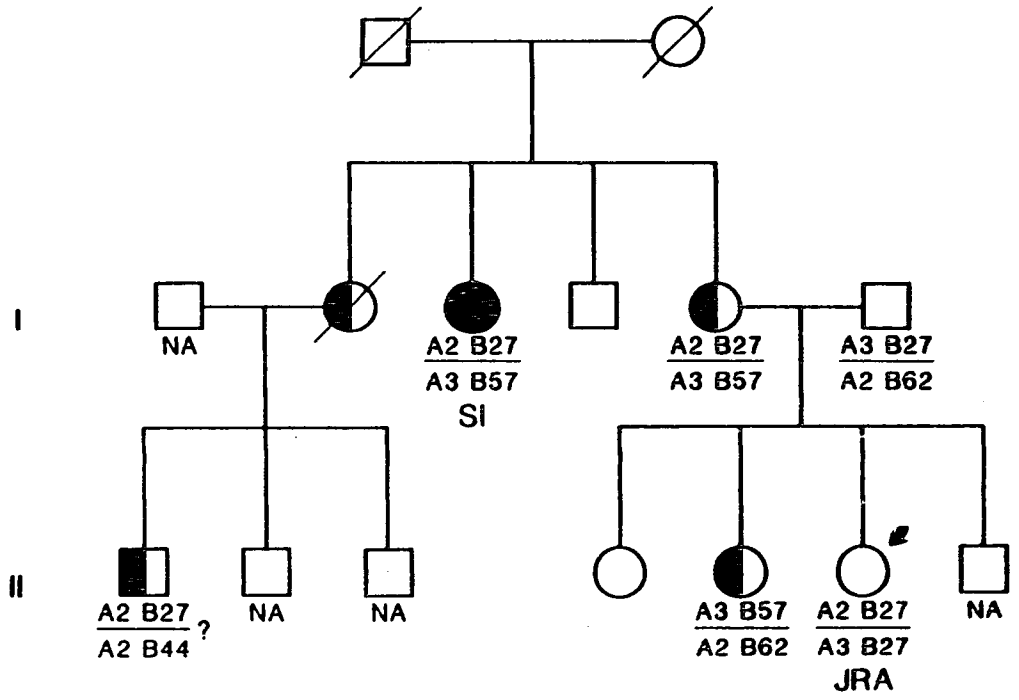
Family 3 (Figure 17)

The proband in this family is a 21 year-old homozygous B27 female with juvenile rheumatoid arthritis and no evidence of psoriasis. She inherited the B27 haplotype from her mother who has psoriasis. One of her sisters inherited the non-B27 haplotype and developed psoriasis. I:2 is an HLA identical sister to the proband's mother, she has both psoriasis and bilateral sacroiliitis. Another deceased sister had psoriasis: her 25 year-old son (II:1) has inherited the B27 haplotype and developed psoriasis with no evidence of AS (no information was available on his father's side of the family).

Family 4 (Figure 18)

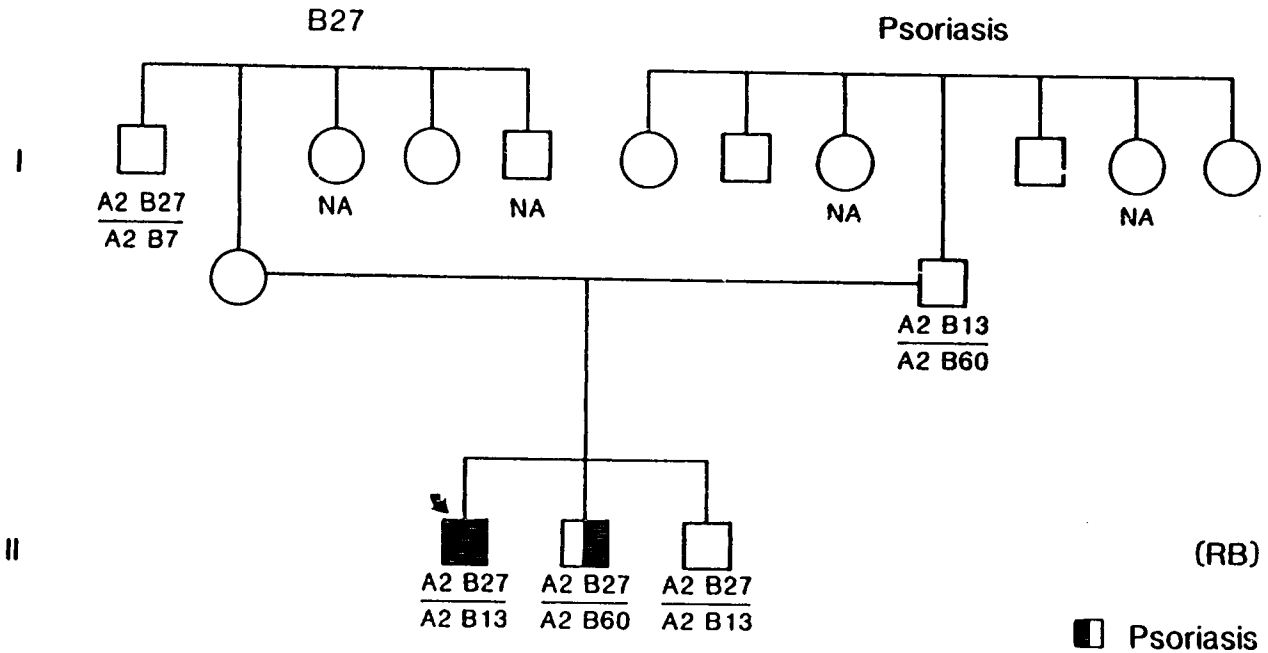
The proband (II:1) is a 30 year-old B27 positive male with AS and psoriasis. His haplo-identical brother is also B27 positive and has AS with no evidence of psoriasis. Both of them inherited a different non-B27 haplotype. None of the other family members studied had psoriasis or AS, however, it was known that psoriasis was a trait in the non-B27 side of the family. We can then assume that the proband inherited both the B27 haplotype and thus the AS from his mother and the psoriasis trait from his father.

FIGURE 17: PSORIASIS, AS AND B27 FAMILY STUDY. PEDIGREE 3



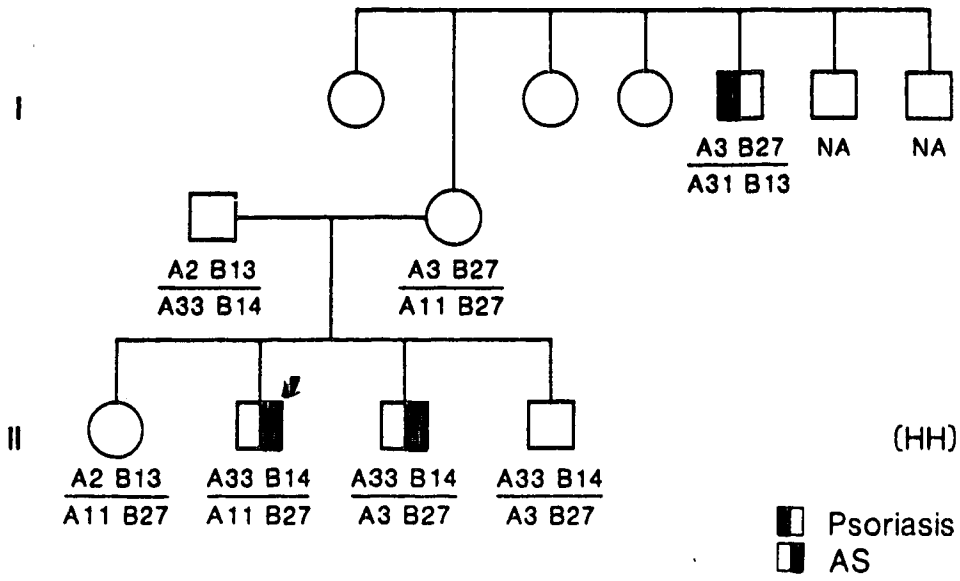
AS: Ankylosing Spondylitis
SI: Sacroiliitis
JRA: Juvenile Rheumatoid Arthritis
NA: Not Available

FIGURE 18: PSORIASIS, AS AND B27 FAMILY STUDY. PEDIGREE 4



AS: Ankylosing Spondylitis
NA: Not Available

FIGURE 19: PSORIASIS, AS AND B27 FAMILY STUDY. PEDIGREE 5



AS: Ankylosing Spondylitis
NA: Not Available

Family 5 (Figure 19)

The proband, II:2, is a 44 year-old male with AS. He carries an A11 B27 haplotype. His 41 year-old brother (II:3) is B27 positive but has a different B27 haplotype (A3, B27) and also has AS. None of them have psoriasis. An uncle (I:5) carries one of the B27 haplotypes and a non-B27 haplotype different from the proband and his brothers: he has psoriasis and no evidence of AS.

B. DISCUSSION

The relationship of the HLA B27 to psoriasis and psoriatic arthritis is still unclear. As mentioned before, from previous studies and from our own experience, the B27 antigen is increased in patients with psoriastic arthritis. The relationship between psoriasis and AS is also obscure. Psoriatic arthritis and AS are both considered related spondyloarthropathies as they share several factors in common: association to the HLA B27 antigen, absence of rheumatoid factors in serum, and spinal arthritis or spondylitis.[30] Clinically and radiologically psoriatic spondylitis appears to be distinct from idiopathic AS which suggests that it may be not an association but a separate disorder.[136-138] Our results presented in Chapter 2 further confirm this hypothesis. We have described 2 different types of spinal involvement in psoriasis: one as part of the clinical spectrum of psoriatic arthritis and the other as an independent occurrence of two separate disorders, AS

and psoriasis. In both cases, HLA-B27 appears to have a role, either by increasing the susceptibility to psoriatic arthritis, or to AS.

To futher define this relationship, we studied a few families where all these factors - B27, AS and psoriasis - were present. In all 5 families the segregation of psoriasis and typical AS appeared to be independent. Thus, patients with both psoriasis and HLA-B27 had relatives with AS carrying the B27 antigen and relatives with psoriasis carrying the non-B27 haplotype. In some cases, family members combined all 3 factors and had both AS and psoriasis with a positive HLA-B27. Only in 1 case (Family 3) two different haplotypes (B27 and non-B27) appeared to be related to psoriasis. This occurred, however, in two cousins: cousins have at least a 50% difference in their genetic background and as we know, psoriasis is a common genetic disorder. Thus, susceptibility genes from different origins may commonly be present in two related families.

Our results further confirmed that psoriasis and AS are in general two separate disorders. As psoriatic arthritis shows an increase in the frequency of HLA-B27, all B27 positive patients with psoriasis and spinal disease are usually considered psoriatic spondylitics. We believe, however, that a thorough clinical examination and family history should be performed to determine whether a particular patient with these characteristics

has concomitant psoriasis and AS or psoriatic spondylitis. Research in psoriatic spondylitis should be done with special care in defining and separating both types of patients. It would also be interesting to perform parallel research in B27 positive patients with AS, AS and psoriasis, and typical psoriatic arthritis and spondylitis to establish if similar or different pathogenetic mechanisms are present in each disorder.

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APPENDIX A

CRITERIA FOR BORDERLINE PSORIASIS (BAKER,1965)

1. Psoriasis of the scalp must be palpable.

2. Mild psoriasis of the scalp simulating dandruff must, in addition, show areas of completely uninvolved skin between the scaly patches.

3. In the presence of eczema, seborrhoea corporis, or seborrhoeic dermatitis anywhere on the body, lesions other than classical plaques on the scalp or elsewhere cannot be accepted as psoriasis.

4. Toe-nail lesions alone cannot be accepted as evidence of psoriasis.

5. Only classical finger-nail lesions of psoriasis, namely: pitting, onycholysis, and the characteristic discoloration of the lateral aspect of the free edge of the nail, can be accepted in the absence of unequivocal psoriasis elsewhere or a definite previous history of psoriasis. In these cases microscopy and culture of the nail should have excluded infection.

6. Flexural lesions in the absence of psoriasis elsewhere are rare and should only be accepted in the presence of other lesions. However, flexural lesions alone may be accepted if they appear classical, i.e. have a sharply defined margin around the whole circumference of all affected areas. Lesions confined to the flexures can only be accepted if microscopy of scrapings has excluded Tinea or Candida infection.

7. Pustular dermatosis of the palms and soles, whether or not conforming to the published descriptions of "pustular psoriasis", cannot be accepted as psoriasis inthe absence of unequivocal lesions of the skin elsewhere or unequivocal nail lesions.

APPENDIX B

NEW YORK CRITERIA FOR THE DIAGNOSIS OF ANKYLOSING SPONDYLITIS

Clinical Criteria

1. Limitation of motion of the lumbar spine in all three planes (anterior flexion, lateral flexion and extension).

2. History or the presence of pain at the dorsolumbar junction or in the lumbar spine.

3. Limitation of chest expansion to 2.5 cm or less, measured at the level of the 4th intercostal space.

Radiological Criteria - Grading of Sacroiliitis

Grade 0 - Normal

Grade I - Suspicious

Grade II - Mild Changes

Grade III - Moderate to Severe Changes including partial ankylosis

Grade IV - Ankylosis

Definite Ankylosing Spondylitis:

Grade III-IV bilateral sacroiliitis with at least one clinical criterion.

Grade III-IV unilateral or Grade II bilateral sacroiliitis with clinical criterion 1 or both clinical criteria 2 and 3.

Probable Ankylosing Spondylitis:

Grade III and IV bilateral sacroiliitis with no clinical criteria.