

PSORIASIS AND ARTHRITIC LESIONS IN RELATION TO THE INHERITANCE OF HLA GENOTYPES: A FAMILY STUDY

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Abstract. This family consists of forty-eight subjects, all of whom have been examined with regard to the presence of psoriasis and nearly all for the presence of arthritic lesions (sacroiliitis and peripheral arthritis). All the members have been tissue-typed not only for HLA-A, B and C locus products but also for D locus products. This has enabled us to study the entire HLA chromosomal region. In the family concerned we have found that those subjects haploidentical with the proband have, to a very large degree, either one or all clinical manifestations, which demonstrates a close genetic relationship between joint (especially sacro-iliitis) and cutaneous manifestations. These findings prompt us to repeat our previously made proposal about different phenotypic expressions of the same genotype. In this family study the disease-associated haplotypes did not contain the genes for B13, 17 or 37 antigens which are known to occur frequently in psoriatic patients. However, not all psoriasis patients have these antigens. Despite that, we believe that the gene(s) which increase the likelihood of developing psoriasis are identical in all patients and therefore family studies where the proband does not carry the particular psoriasis associated B-alleles are equally illuminating as to the inheritance pattern of disease.

Genes within the HLA-region of chromosome no. 6 display that phenomenon called linkage disequilibrium, which means that specific HLA antigens which are products of different loci occur more often together than expected from the individual gene frequency of each HLA specificity. This forms the basis for the associations between HLA antigens and various diseases (2).

The list of associations between specific HLA antigens and disease is increasing. As regards psoriasis, the first report (which appeared in 1972) demonstrated that HLA B13 and B17 were more frequent in patients with psoriasis (32). These findings have since been confirmed and new specificities have been added (29). Recently HLA -BW16, BW37, CW3, CW6, DW7 and DW8 have been shown to occur more frequently among

psoriasis-affected patients (14, 17, 18, 28, 30, 31). HLA-B27 is the specificity which shows a striking association to any disease. Thus, ankylosing spondylitis and pelvospondylitis display a uniquely strong association with B27. We (as well as others) have also found that the seronegative arthritis which includes the arthropathy connected with psoriasis is associated to B27, in contrast to the association to DW4 in rheumatoid arthritis (8, 18, 24, 25). The reason for these associations is not clear but it is mostly suggested by analogy from experimental species, that the HLA-region contains specific IR (immune response) genes and IS (immune suppressor) genes, occurring in linkage disequilibrium with specific HLA-B and D alleles. These and other possible mechanisms have been discussed by Zinkernagel & Amos (1, 33). Other products governed by genes in the HLA region have been implicated, such as defects in complement factors (10).

Furthermore it has recently been suggested that some HLA molecules may have structures similar to that of receptors for hormones and thus could cause competition between these structures and the physiological ligand (29).

In previous investigations we have found that arthritic and cutaneous lesions in a psoriatic family appeared as different clinical manifestations in subjects with the same haplotype as the proband (20). The present study was undertaken to study this relationship further. It should be stressed that we have included the D-locus in our study. This means that we encompass a wider part of the HLA region than if only A, B and C locus products had been included.

MATERIAL AND METHODS

The family selected for this study consists of 48 subjects belonging to three generations. The clinical and radiologi-

Table 1. The clinical parameters and laboratory data of all members of the family

Individual	Age	ESR ^a	RF test ^b	ANF ^c	Pso-riasis	Sacro-iliac joints ^d	Peripheral arthritis (see text)	Arthralgia (see text)	Radiological examination of peripheral joints ^e
I: 2	71	7	1/64	—	—	3/3	—	—	H
I: 4	76	35	1/128	—	+	2/2	—	—	H, F
I: 7	76	34	—	ND ^f	—	0/0	—	—	ND
I: 9	71	2	—	ND	—	0/0	—	—	ND
I: 10	74	26	1/8	—	—	3/0	—	—	H, F
I: 12	69	38	1/32	—	—	0/0	—	+	H, F
II: 1	51	9	—	—	—	3/3	—	—	ND
II: 2	47	8	1/32	—	+	1/0, OC ^g	+	+	H, F
II: 3	40	13	1/32	—	—	3/3	—	+	H, F
II: 4	41	10	—	—	—	3/3	—	—	ND
II: 5	56	7	—	—	—	0/0	—	—	H, F
II: 6	49	9	1/8	ND	—	3/3	—	—	ND
II: 7	47	30	1/16	ND	—	3/3	+	+	H, F
II: 8	45	18	1/8	ND	—	0/0, OC ^g	—	—	ND
II: 9	39	2	—	—	+	3/3	—	—	ND
II: 10	41	ND	—	—	+	0/0	—	—	H, F
II: 11	30	3	—	ND	—	2/1	—	—	ND
II: 12	51	1	—	—	—	1/1	ND	—	ND
II: 13	50	ND	ND	ND	+	ND	ND	—	ND
II: 14	43	3	—	—	—	3/3	—	—	H, F
II: 15	42	14	—	—	—	0/0	+	+	H, F
II: 17	49	8	1/16	—	—	3/3	—	+	H, F
II: 18	52	1	—	—	—	0/1	—	+	H, F
II: 19	49	8	1/16	—	—	3/3	—	+	H, F
II: 21	53	13	1/16	—	—	0/9	+	+	H, F
III: 1	25	9	1/128	—	—	3/2	—	—	ND
III: 2	23	5	—	—	—	3/2	—	—	ND
III: 3	19	6	1/16	ND	—	3/3	—	—	ND
III: 4	24	22	1/16	ND	+?	3/2	—	+	H, F
III: 5	16	21	1/8	ND	+	3/3	+	+	H, F
III: 6	6	ND	ND	ND	—	ND	—	—	ND
III: 7	22	1	—	—	—	0/0	—	+	ND
III: 8	26	2	1/32	—	+	0/0	—	+	H, F
III: 9	30	2	1/8	—	—	0/1	—	—	ND
III: 10	28	6	—	—	—	0/1	—	—	ND
III: 11	12	ND	ND	ND	—	ND	—	—	ND
III: 12	19	5	—	—	—	3/3	—	—	H, F
III: 13	17	7	—	—	—	3/3	—	—	H, F
III: 14	28	11	—	—	—	0/1	—	—	ND
III: 15	24	29	—	—	—	1/0	—	—	ND
III: 16	27	3	1/64	—	—	3/1	—	—	ND
III: 17	27	17	—	—	—	3/3	+	+	H, F
III: 18	30	11	—	—	+	3/3	—	+	ND
III: 19	19	3	—	ND	—	2/1	—	—	ND
III: 20	17	5	—	—	—	3/3	—	+	H, F
III: 21	17	7	—	—	+	3/2	—	—	H, F
III: 22	26	4	—	—	—	3/2	—	—	ND
III: 23	24	2	ND	—	—	0/0	—	—	ND

^a ESR=erythrocyte sedimentation rate.^b RF test=rheumatoid factor test.^c ANF=antinuclear factors.^d R/L=right/left. For grading of the lesions of the sacro-iliac joints, see text.^e H=hands, wrists; F=feet, ankles.^f ND=not done.^g OC=osteitis condensans.

Table 11. The "arthralgia group"

R=right; L=left; IP=interphalangeal joints; MCP=metacarpophalangeal joints; MTP=metatarsophalangeal joints; PIP=proximal interphalangeal joints

Subject	Joints affected	Side
I: 12	MTP II-III	R/L
II: 3	Knee	R
II: 17	PIP	R/L
II: 18	Knee, MCP	R/L
II: 19	Wrists, IP	R
III: 4	Knee	R/L
III: 7	Wrist	R/L
III: 8	Wrist, PIP	R/L
III: 18	Knee	R
III: 20	Wrist, MCP IV	L

cal evaluations have been made independantly by the different investigators without knowing anything about the tissue typing results.

Evaluation of the skin. The examination of the skin for the presence of psoriasis and subcutaneous noduli was made in all subjects by J.M., who also has initiated the study. Special attention has been paid to the scalp, nails, elbows, buttocks, knees and the perianal area. For borderline cases the criteria formulated by Baker were adopted, with some modifications (3). According to Baker it was originally stated that mild psoriasis of the scalp simulating dandruff must, in addition, show areas of completely uninvolved skin between the scaly patches. We registered individuals with mild dandruff only if the scales were organized in patches, if they were palpable and if the skin below was affected. All the subjects were questioned regarding symptoms indicating iritis.

Evaluation of the joints. The clinical evaluation of the joints was done by L.R. according to the criteria used by Lars Molin (23). These were based on the New York criteria of 1966, but some modifications were made to fit the present situation (6). Our criteria are summarized below:

1) A history, past or present, of joint pain, without stipulation as to duration. Tenderness on palpation.
2) Involvement by swelling (soft tissue thickening or effusion, but not bony overgrowth alone), limitation of motion, subluxation or ankylosis.

3) A history of arthritis according to criterion no. 2 noted and treated by doctor, as could be read from case reports or by relevant information from the patient or from the relatives.

4) Definite erosive changes on the radiographs.

The following joints are excluded: first carpometacarpals, hips and first metatarsals. Subluxation of the lateral metatarsophalangeal joints must be irreducible. In all instances the affection of one or more joints was taken into consideration.

Joints that occur in groups such as the proximal interphalangeal joints or metacarpophalangeal joints should only be counted as a single joint on the same side. The genetic discussion will only be based on those individuals fulfilling criteria 2-4. Nevertheless, all fulfilling criterion

no. 1 will be registered but not included in the final account.

When peripheral joints are mentioned later on, we mean the joints of the extremities with the above-mentioned exceptions.

Radiological examination. Radiographs of peripheral joints (hands and feet including wrists and ankles) were taken in nearly all individuals with clinically affected joints (past or present) using standard projections (6, 15).

Radiological examinations of the sacro-iliac joints were made in two projections:

1) Anterior-posterior with the tube tilted 25 degrees caudally and the patient supine.

2) Posterior-anterior projection with the patient lying prone.

The radiograms of the peripheral joints were interpreted by N.L. according to the atlas of Kjellgren and grading of changes of sacro-iliac joints according to the New York Criteria (6, 15). Thus grade 2 or higher of radiological changes of the sacro-iliac joints was recorded as positive for the further analysis, irrespective of whether the lesions were uni- or bilateral.

Laboratory investigations

Nearly all the subjects were tested for the presence of rheumatoid factor, using the sensitized sheep cell haemagglutination test (26). A titre $\geq 1/128$ was considered positive. The presence of antinuclear factor was determined as well (7). A titre $\geq 1/25$ is regarded as positive.

Tissue typing

Definition of HLA -A, B and C locus products. Purification of lymphocytes and typing for HLA A, B and C locus product was done as described previously (16).

The following specificities were tested:

HLA-A: 1, 2, 3, 10, (W25, 26) 11, 28, W19, (W29, W30-31, W 32).

HLA-B: 5, 7, 8, 12, 13, 14, 17, 27, W15, W16, W18, W21, W22, W35, W37, W40, W41.

HLA-C: W1, W2, W3, W4-7.

Definition of D locus products. The D-alleles were defined with the aid of cellular methods.

1) Intrafamilial mixed lymphocyte culture (MLC) technique was employed in order to unspecifically define D-locus products (20).

2) For specific definition of D locus products (LD-typing), homozygous typing cells were used. The following specificities were tested: DW1, DW2, DW3, DW4, DW5, DW6, DW7 and DW8.

3) For both specific and unspecific definition of D locus products primed lymphocyte typing (PLT) was employed.

In some instances highly selected antisera defining B-cell antigens were used. Results and interpretation of laboratory data will be presented elsewhere (21). In those instances where we have not been able to specifically define the D-alleles, small letters are used for their designation.

RESULTS

All the clinical data are summarized in Fig. 1 and Tables I and II.

Cutaneous manifestations

Nine individuals displayed unequivocal signs of psoriasis. (I: 4, II: 2, II: 9, II: 10, II: 13, III: 5, III: 8, III: 18 and III: 21). Individual I: 8 has been noted as probably psoriatic, from hearsay. The woman III: 4 has been recorded as psoriatic by the district doctor but displayed no signs of psoriasis on examination. No subcutaneous nodules and no ocular symptoms could be detected.

Arthritic lesions

44 members of the family have been clinically examined with particular regard to involvement of peripheral joints. Two refused to participate in this part (II: 12, II: 13) and two (III: 6, III: 11) were too young for radiological examination. Nineteen subjects showed some kind of joint involvement. In 10 subjects (Table II) we found symptoms fulfilling criterion no. 1, i.e. joint pain and/or signs in the form of tenderness on palpation of peripheral joints. Three individuals (I: 2, I: 4, I: 10) fulfilling criterion no. 1 were excluded on account of radiological signs of degenerative changes without erosions, typical of osteoarthritis, in the clinically affected peripheral joints. Six had a history of/for clinical signs of arthritis (criterion nos. 2-4) of peripheral joints and will be described in detail. Laboratory and clinical data (Table I) are only mentioned below when considered relevant.

II: 2. Psoriasis for 25 years. During the last 10 years, symptoms in the form of swelling and tenderness of wrists and finger joints. On admission to hospital in 1970, synovitis of the metacarpophalangeal joints of the right hand and knee, flexion contractures in some fingers of both hands.

Radiological examination: well defined areas of erosions in some interphalangeal joints. Swan-neck deformity of third and fourth fingers of right hand. Extension defects of the proximal interphalangeal joints of third finger of both hands.

Comment. Diagnosis consistent with the nosological entity psoriatic arthritis and psoriasis.

II: 7. Pain and swelling of the joints of her legs for 25 years. Hospital treatment for polyarthritis. Periodical swelling of the proximal interphalangeal joints of both hands. Tenderness on palpation over the wrists. No signs of psoriasis. Radiograms of the peripheral joints: no abnormality.

Comment. Sacro-iliitis and a history of polyarthritis.

II: 15. Signs of soft tissue swelling of the third left

metacarpophalangeal joint, pain on movement and slight dorsal-flexion defect in the right wrist. X-ray of the peripheral joints: normal. No signs of psoriasis were detected. The stepsister has psoriasis.

Comment. Seronegative oligo-arthritis.

II: 21. Complaining of symptoms from the joints for 30 years. Intermittent arthralgia and morning stiffness of the proximal interphalangeal joints in both hands. Mild symptoms throughout the years.

Signs of synovitis of the second digit of the left foot, pain on movement and tenderness on palpation over shoulder joints. Radiographs of peripheral joints: no erosions, but degenerative changes in some joints.

Comment. Mild seronegative chronic arthritis.

III: 5. Joint symptoms that started 6 months prior to the examination. Arthralgia of both hands. Soft tissue swelling of the metacarpophalangeal joints of third finger of both hands. Radiological examination: no abnormalities of the peripheral joints. Six months after examination she developed psoriasis.

Comment. Seronegative polyarthritis, sacro-iliitis and psoriasis.

III: 17. At the age of 11, hospital treatment for pain in the knees and shoulder joints following tonsillitis. For a long time afterwards, arthralgia of shoulders, wrists and ankles. Re-admitted to hospital at the age of 14 with slight swelling and tenderness over the wrists as well as tenderness on palpation over several peripheral joints. Recurrence in 1976, with pain and swelling of the right knee and shoulder. Radiograms of hands and feet: no changes.

Comment. Sacro-iliitis and past history of seronegative arthritis.

HLA genotypes

The results of the serological definition of HLA-A, B and C locus antigens and the MLC experiments for definition of D-locus specificities are given in Fig. 1. For the problems concerning the definition of the D locus antigens and experimental details, see Marcusson & Möller, 1978 (21).

One possible recombinant event (III: 22) and 2 definite cases (III: 7, III: 13) were found in this family. Subject III: 7 has inherited an HLA A/C recombinant chromosome from his mother and individual III: 13 an HLA B/D recombinant paternal chromosome. Concerning III: 22, see Marcusson & Möller (21).

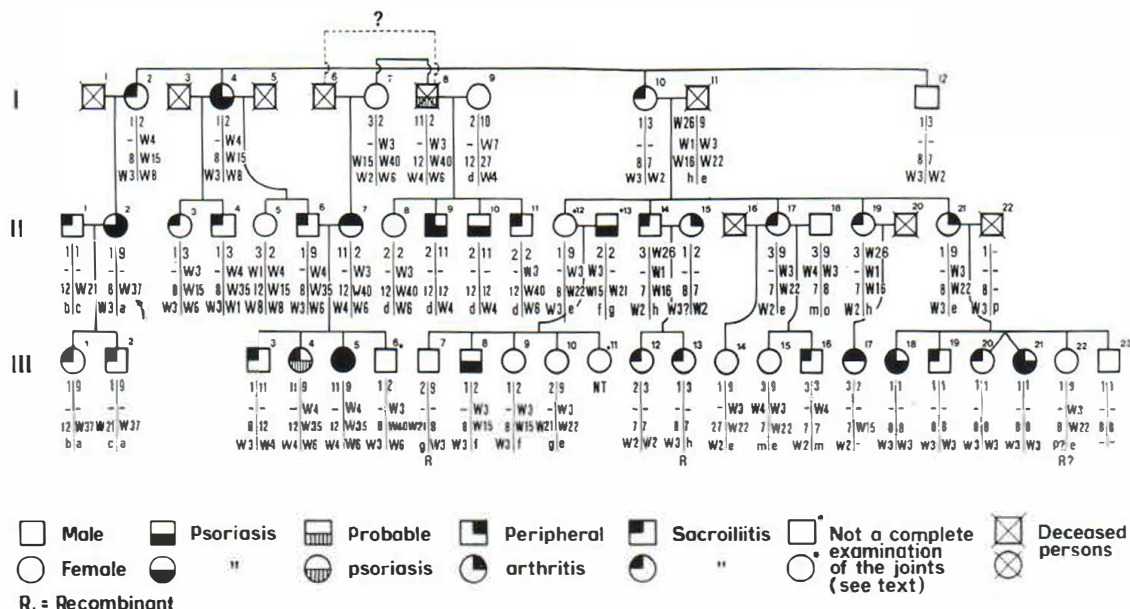


Fig. 1. Pedigree. The HLA antigens A, C, B and D are given from top to bottom in the same order as they are charted on the 6th chromosomes. Lower case letters are used to designate the D-locus markers in those instances

where they have been unspecifically defined. In the other instances the appropriate denomination has been used. A dash shows that the corresponding specificity has not been defined. Concerning I: 10, see note added in proof.

The pedigree

The proband (II: 2) having the genotype A1, C-, B8, DW3/A9, c-, BW37 Da (the prefixes A, C, B and D will be omitted hereafter and the specificities are presented in the same order as on the HLA region of the 6th chromosome) is suffering from psoriasis and peripheral arthritis. One of her haplotypes, 1,-,8, W3, is found in her mother I: 2, who has sacroiliitis. Her HLA identical sister I: 4 revealed unequivocal signs of sacro-iliitis upon X-ray and a past documented history of psoriasis. Thus the hitherto described psoriatics share the haplotype 1,-,8, W3. The four offspring of I: 4 have provided us with further important information. Three with the haplotype 1,-,8, W3 (II: 3, II: 4, II: 6) are affected by sacro-iliitis and II: 5, registered as healthy, have the other maternal haplotype.

In I: 10 only sacro-iliitis could be found, in contrast to her HLA identical brother (I: 12) who, by our criteria, is considered healthy. Both are haplo-identical with the proband. Of her five children (II: 12, II: 14, II: 17, II: 19 and II: 21) 4 are afflicted either by sacro-iliitis alone or by peripheral arthritis. However, the peripheral joints of the subject (II: 12) have not been completely clinically

evaluated (Table I). These findings are confusing as those affected are carrying either haplotype of their mother (I: 10). On proceeding to the third generation, the pattern will become clearer.

First we will consider those individuals with the 1,-,8, W3, then those with the 3,-,7, W2 haplotype. The subject II: 21 (Haplotype 1,-,8, W3) has given birth to 6 children, 5 of whom are haplo-identical with the proband. Four of them are HLA homozygous and afflicted by disease as well. Two have psoriasis and sacro-iliitis (III: 18, III: 21) and 2 have sacro-iliitis (III: 19, III: 20). Individuals III: 20 and III: 21 are twins, but are not monozygotic. Among the descendants of II: 12 and II: 13 only one (III: 8) has been found to suffer from psoriasis. The others appear healthy. As the father (II: 13) has psoriasis and we have no information about his relatives his contribution to his children is difficult to evaluate. In summarising this part it can be stated that out of 18 individuals with the B8 containing haplotype, 5 are affected with psoriasis. If the joint-affected subjects are included, altogether 13 subjects are suffering from some kind of disease and sacro-iliitis is the most frequent disease manifestation.

The other descendants of individual I: 10 in the second and third generation, who have the haplotype 3,-,7,W2 help us to resolve the problem that the affected offspring have different haplotypes. This subjects III: 12 and III: 13 are both carrying the whole or a part of the 3,-,7,W2 haplotype (III: 13 has a HLA B/D recombinant chromosome and III: 12 the complete paternal haplotype), and both of them have sacro-iliitis. Their mother (II: 15) has peripheral arthritis and is related to a psoriatic who, however, was not available for this study. Of the three offspring of subject II: 17 the one (III: 16) who carries the 3,-,7,W2 haplotype has sacro-iliitis. The other two, of whom one (III: 14) is a half-sister, are healthy.

Individual II: 19 has sacro-iliitis and her daughter (III: 17) has both her sacro-iliac and peripheral joints affected. Both of them are 3,-,7,W2 carriers. Thus 8 out of 9 carriers of the 2,-,7,W2 haplotype (including the B/D recombinant, II: 13) are affected by some kind of arthritis.

Let us return to the left part of the pedigree and the couple II: 6 and II: 7 and their offspring. In this part of the family, 2 HLA identical daughters (III: 4, III: 5) have signs of disease. One is registered as a probable psoriatic and the other as a definite psoriatic, both with sacro-iliitis and one with peripheral arthritis as well. The son (III: 3) only displays signs of sacro-iliitis. This pattern seems confusing, as the afflicted are not haplo-identical with the proband, but as the mother (II: 7) is suffering from both sacro-iliitis and peripheral arthritis the disease-predisposing genes are most likely conferred by her 11,-,12,W4 haplotype which is to be found in 3 of her children. The haplotype 11,-,12,W4 is furthermore found among the maternal cousins (II: 9 and II: 10), both suffering from psoriasis. This haplotype derives from the deceased father I: 8 who, from hearsay, had psoriasis. He was probably related to I: 6, as their ancestors lived for many generations in an isolated village in northern Sweden.

Since the 11,-,12,W4 haplotype is very rare, we believe it to be the same in II: 7 and II: 10 (13, 21). Thus this haplotype also seems to be a disease-associated haplotype.

DISCUSSION

A well recognized fact in the field of HLA and disease is the statistical association between psoriasis and HLA-B13 and B17. Additional specificities such as HLA-BW37, CW3 and CW6 have

also been shown to be more frequent among psoriasis patients than in controls (4, 14, 17, 18). Recently certain D-locus specificities have been added to the list (30). In a large study on the inheritance of psoriasis it was found that the frequency of psoriasis among first-degree relatives was twice as high for probands carrying the HLA-B13, B17 and BW37 antigens as among probands lacking these antigens (27). From our own family investigations we have found a high frequency of psoriasis in individuals having the same haplotype as the proband (20). The most likely interpretation of these data is that if more than two genes are involved in the pathogenesis of disease (28) as has been implied, these genes are most likely present on chromosome no. 6. The exact localisation of these genes is at present not known. Thus it is not clear whether all the genes are situated inside and/or outside the HLA-region. If other non-HLA-linked genetic factors are of importance, as other studies tend to indicate, then these genes may have only a modulating influence on the outcome of disease (4, 5). The penetrance of psoriasis in the families presented is not complete, for reasons not exactly known. If environmental factors are to be implicated in the pathogenesis of psoriasis, it is possible that not all the individuals carrying the disease-susceptibility genes have met with this particular factor (or factors). Alternatively, other genes situated on the 6th chromosome—or on other chromosomes—may have a restricted or perhaps enhancing influence on the development of disease.

Another possibility is that cutaneous lesions in psoriasis may be only one disease manifestation among several, a problem which has not been seriously considered previously (22). As arthritic lesions—especially sacro-iliitis—are more frequent among psoriatics, we decided to investigate these clinical parameters in relation to the inheritance of the HLA genetic markers (23).

Our first published families (19, 20) showed that when we included all subjects affected by some signs of disease, including those individuals complaining of joint symptoms, we found a high penetrance of disease in those family members which were haplo-identical with the proband. These family investigations gave impetus to further investigation on the relationship between cutaneous and joint manifestations. It should be pointed out that in our investigations the whole HLA region has been investigated, e.g., we have included the D-locus.

The present family is one of several families investigated. The proband (II: 2) has psoriasis and peripheral arthritis and the genotypes 1,-,8,W3/9,-,W37.a. (The prefixes A, C, B and D have been omitted. The specific alleles are presented in the order mentioned.) It is consequently noticeable that, although BW37 is the B-allele which in association studies occurs more often among psoriasis patients, it is the 1,-,8,W3 haplotype which is found in the maternal aunt, who suffers from psoriasis and sacro-iliitis. This haplotype is found in altogether 20 subjects, including one A/C recombinant. When psoriasis alone is considered, 5 are affected; when the patients with arthritic lesions are included, 14 are afflicted by either psoriasis and/or arthritis (peripheral arthritis and sacro-iliitis). Affection of the sacro-iliac joints, however, is the most predominant clinical trait. The fact that the 1,-,8,W3 haplotype really is a disease-predisposing haplotype is underlined when the children of I: 4 are considered. In this sibship it can be shown that all those who have the B8 allele displayed unequivocal radiological signs of sacro-iliitis. The healthy individual II: 5 has the other maternal haplotype and she has reached the age of nearly sixty. The probability therefore that she will develop a disease still exists, of course, but it is less likely. She therefore makes a good control.

However, some findings in this study complicate the interpretation. The young boy III: 8 has psoriasis and the 1,-,8,W3 haplotype, but since his father has psoriasis, his genetic contribution is difficult to evaluate. Nothing is known about his relatives, and consequently it is not possible to assign the disease-predisposing genes to any one of his haplotypes.

The maternal aunt I: 10 appears to have disease-predisposing genes on both her haplotypes, since all her descendants with the 3,-,7,W2 haplotype are affected by disease. In this case, however, only arthritic lesions are the HLA-linked traits and the carriers seem to have an early début. That this is so is strengthened by the fact that those individuals who do not have that particular haplotype (III: 14 and III: 15) are healthy. Furthermore one of them is a healthy carrier of the B27 allele known to be associated with arthritic lesions. The penetration of disease among the 3,-,7,W2 carriers is 7 out of 8.

In the sibship III: 3-III: 6, 3 members are disease affected. The two HLA identical sisters are both suffering from psoriasis and arthritis. Their mother

suffers from both axial and peripheral arthritis and she has conveyed to her 3 affected children the 11,-,12,W4 haplotype. It is likely that this haplotype carries disease susceptibility genes. This statement is supported by the finding of the same haplotype in the maternal cousins II: 9 and II: 10, both of whom have psoriasis. It has previously been discussed that I: 6 and I: 7 are probably related. Thus we may well have a third disease-predisposing haplotype, since all living carriers are disease affected. The boy III: 3 therefore most probably has disease susceptibility genes on both his haplotypes.

In the sibship II: 8-II: 11, there is one more affected by sacro-iliitis. However, we do not have a complete knowledge of the occurrence of disease in his ancestors on both sides and it is therefore difficult to fit him into the hereditary pattern of the rest of the family. The same comment is also valid for II: 1 and his 2 children (III: 1, III: 2).

From this it follows that the traits studied are most probably dominantly inherited and that the disease-predisposing genes are to be found within and/or in close proximity to the HLA region. It is quite obvious that there exists a genetic relationship between cutaneous and arthritic lesions in this family, but the true nature of this relationship is not known. Whether it is due to identical HLA linked gene(s) or whether distinct but closely linked gene(s) are operating, each responsible for its own clinical symptom, cannot be settled as yet. Because of the distribution of disease in the family it is justified to repeat our previous suggestion about different phenotypic expressions of the same genotype, e.g. cutaneous and arthritic lesions are alternative clinical manifestations of a single genetic predisposition in one and the same individual.

In this family we have two patterns of disease presentation—two haplotypes associated with both cutaneous and joint manifestations and one haplotype associated with arthritis only. Comparison of these two patterns can be put forward as an argument that distinct but closely linked genes are involved, each responsible for its own clinical feature. Thus the 1,-,8,W3 and 11,-,12,W4 haplotype should contain separate though closely linked genes involved in the pathogenesis of psoriasis, peripheral arthritis and sacro-iliitis. The 3,-,7,W2 haplotype on the other hand should only contain genes whose products should be responsible for the mechanisms producing arthritic lesions. This question cannot be solved with our present

knowledge and it should be remembered that clinical evaluation is a very coarse method which only discovers signs but not the underlying mechanisms. This means that identical clinical features may have different etiologies. Therefore the search for common pathogenetic mechanisms must go on.

Immunofluorescence studies on synovial membranes of psoriatic arthritis, compared with the findings in rheumatoid arthritis, have shown that complement factor C3 was lacking in psoriatic arthritis but present in rheumatoid arthritis (11). This demonstrates that the mechanisms may be different and research along these lines would perhaps reveal common pathogenetic pathways in cutaneous and joint affection. Scintigraphic investigations have furthermore shown a pathological uptake of radionuclide in the joints of a large proportion of psoriatics, even in those who had no complaints of joint affection. This further substantiates our concept of a close relationship between the studied traits (12).

The present study illustrates the value of family investigations for the further elucidation of associations between HLA and disease. Psoriasis is associated with the B antigens, 13, 17 and W37 as well as with the C antigen W6 and with some D antigens (27, 28, 30). However, there are psoriasis patients who have none of these antigens. These findings suggest that the psoriasis-predisposing gene(s), if present within the HLA chromosomal region and thus linked to HLA, is (are) not identical with the genes for any of these HLA antigens, but rather occurs in linkage disequilibrium with these genes. The implication of these data will be further discussed elsewhere (21). In this family none of the specific antigens could be found. In our opinion, all patients who develop psoriasis have identical disease-predisposing genes. Therefore family studies, where the proband's disease-associated HLA haplotype does not carry any of the above-mentioned alleles, are equally informative as to the inheritance pattern of psoriasis, as family studies where the proband's disease-associated haplotype does contain one of the above-mentioned antigens.

We believe that the observed decreased frequency of the B antigens 7, 8 and 12 compensates for the increase in other B antigens (5, 9).

Finally, we are well aware of that a study such as the present one only gives a fleeting picture of the distribution of disease among the family members. This means that any individual, especially of the

third generation, may be in great danger of developing a disease, which may thus either confirm or refute the presented interpretation.

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NOTE ADDED IN PROOF

During the editorial preparation of the manuscript, which took place two years after the physical examination of the family members, individual I: 10 developed seronegative polyarthritis. Small and big joints of the extremities in a symmetrical distribution showed soft tissue swelling, effusion, tenderness on palpation and pain on movement. This event furthermore substantiate the above presented interpretation.

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