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GENETIC MARKERS IN PSORIASIS

Correlations to Age at Onset, Continuity of Symptoms and the Risk of Developing the Disease

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Abstract. In a study on genetic markers (22 HLA antigens, 6 blood group types, 3 serum groups and 3 red cell enzymes) in psoriatic patients the following statistically significant differences were found between patients and controls: 1) The HLA factors B13 and Bw17, the Lewis blood group Le(a−b−) and the blood group factor A were overrepresented among the patients. A decrease in the frequencies of the HLA factors B7 and B8 was noted, confirming several similar findings by other investigators. 2) In the Ss (MNSs), C3 and haptoglobin (Hp) systems the psoriatic patients showed a decreased frequency of heterozygotes. 3) Among patients with continuous symptoms the blood group factor A and the blood group Fy (a+b−) were overrepresented. 4) Patients with late onset of psoriasis showed an increase in the blood group (Fy(a+bb−) and a decrease in the haptoglobin type 2-2.

Relative risk figures have been calculated for different phenotypes. Certain genetic combinations were found to be grossly overrepresented among the patients. The mechanisms behind the associations appear to differ. In three systems (Ss, C3 and Hp) the deviations in psoriatic patients suggest the presence of heterozygote advantage.

Key words: Psoriasis; HLA antigens; Blood groups; Serum groups; Red cell enzyme types; Disease association

The importance of genetic factors in the development of psoriasis and the mode of inheritance of this disease have been the subject of many studies in the past. Both dominant and recessive modes of inheritance have been proposed. It has been difficult to reconcile the results obtained with these hypotheses, however. For literature references on this subject, see (1). A more likely explanation is that psoriasis is a polygenic and multifactorial disease (6, 15, 16).

Diseases with a multifactorial background may be caused by environmental and genetic factors in combination. Polygenic diseases result from the combined effect of genes at different loci. Thus a number of different genes may influence the risk of an individual to develop a particular disease by bringing the individual closer to the threshold beyond which manifestations of the disease begin to appear. Associations have been demonstrated between certain factors in the human major histocompatibility locus (HLA factors) and various diseases. Among the dermatological diseases, psoriasis is of special interest in this context (for a review, see 14). Three HLA antigens, B13, Bw17 and Bw37, have been found in increased frequencies in psoriasis vulgaris. Individuals carrying combinations of these three factors do not run any increased risk of developing the disease (13).

In a previous report (3) we have confirmed the association with B13 och Bw17, and demonstrated associations between psoriasis and certain antigens in the ABO, MNSs and Lewis blood group systems. On the basis of these findings, we have studied associations between genetic markers and two clinical parameters, viz. the age at onset and the continuity of symptoms as well as the relative risks of developing psoriasis in individuals with different genetic combinations.

MATERIAL AND METHODS

The population series studied was collected randomly amongst both out-patients and in-patients having psoriasis vulgaris. The sex distribution was 52% males and 48% females. The mean age was 45.6 years, with a range of 13 to 82 years. Ten patients had concomitant arthritis.

The methods for the determination of the genetic markers have been presented earlier (3). It was not possible to

Table I. *HLA antigens in 87 psoriatic patients and 198 controls*

Antigens	Patients		Controls	
	n	%	*n*	%
A1	24	27.6	52	26.3
A2	61	70.1	121	61.1
A3	25	28.7	62	31.3
A9	9	10.3	39	19.7
A10	3	3.4	19	9.6
A11	4	4.6	23	11.6
Aw19	9	10.3	32	16.2
A28	15	17.2	27	13.6
B5	8	9.2	22	11.1
B7	21	24.1**	82	41.4
B8	13	14.9*	50	25.3
B12	23	26.4	57	28.8
B13	6	6.9**	2	1.0
B14	0	0.0	0	0.0
Bw15	22	25.3	44	22.2
Bw17	9	10.3***	1	0.5
B18	1	1.1	10	5.1
Bw21	2	2.3	2	1.0
Bw22	1	1.1	6	3.0
B27	22	25.3	38	19.2
Bw35	10	11.5	25	12.6
Bw40	18	20.7	41	20.7

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

study all the markers in all patients, and consequently the number of patients examined varies from system to system. In all systems but two, more than 100 patients were tested. The exceptions are the HLA system where complete testing was feasible in 87 patients only and the Lewis blood groups where 93 patients were typed.

The time of onset and the severity of the disease were, when possible, determined in retrospect from the hospital records of the patients. In other instances this information was obtained direct from the patients by means of a questionnaire. Onset was classified as 'early' up to 19 years of age and 'late' from 20 years and onwards. Severity was defined in terms of continuity of the symptoms. Patients were classified into two groups; those with continuous symptoms and those having symptom-free periods (intermittent type). In 6 patients the information obtained was insufficient for a safe classification.

The HLA terminology conforms with that used by Svejgaard et al. (13). Statistical analysis was performed by means of the Chi-square test.

RESULTS

The results of HLA typing of 87 patients and of 198 non-psoriatic controls are shown in Table I. The frequencies of antigens B13 and Bw17 were significantly increased, whereas those of antigens B7 and B8 were significantly decreased. In the control material the frequencies of Bw17 and B13 were comparatively low and B27 higher than is usually reported in Caucasian populations.

The frequencies of the MNSs blood groups showed marked differences between patients and controls. It was found that these differences could be ascribed to deviations in the Ss factors. The frequency of the SS type was significantly ($P<0.001$) increased and that of the Ss type was significantly ($P<0.001$) decreased among the patients.

The frequency of blood group Le(a−b−) was significantly increased in the psoriatic patients, compared with the controls ($P<0.001$).

In three systems (ABO, C3 and Hp) the patients showed less pronounced deviations from the corresponding control materials. The frequency of the A factor (blood groups A and AB) was higher in the patients than in the controls ($P<0.05$). In the C3 system a significant deficiency of FS heterozygotes ($P<0.025$) was found among the patients. In the haptoglobin system too a significant heterozygote deficiency (Hp 2-1) was found among the psoriatic patients ($P<0.025$). In the other marker systems (Rh, Kell, Duffy, Gc and red cell enzymes) no differences were found between the patient material and the controls.

Of the marker systems in which associations with psoriasis were found only the ABO system showed a statistically significant association with continuity of symptoms (Table II). The frequency of blood group factor A was increased ($P<0.05$) and that of

Table II. *Associations between markers and continuity of psoriatic symptoms*

Marker system	Type of psoriasis: Continuous No.	%	Intermittent No.	%	*P*
ABO					
Total	65		44		
A	37	57	18	41	
B	7	11	4	9	
AB	6	9	2	5	
O	15	23	20	45	<0.025
A-factor	43	66	20	45	<0.05
Duffy					
Total	63		43		
a+b−	17	27	3	7	<0.01
a+b+	29	46	25	58	
a−b+	17	27	15	35	
Fy^a gene	63	50	31	36	<0.05

blood group O decreased ($P<0.025$). Continuous symptoms were also associated with the Duffy blood group Fy(a+b−) ($P<0.01$).

The associations with age at onset have been summarized in Table III. Patients with late onset showed an increase ($P<0.05$) in the frequency of the Duffy blood group Fy(a+b−) and a decrease ($P<0.05$) in the frequency of the haptoglobin type Hp 2-2.

In Table IV relative risks are given for four different phenotypes, which are significantly overrepresented among psoriatic patients. In the HLA system, individuals with the B13 and Bw17 antigens have been considered as one risk group, since these two antigens have similar risk values and combinations or homozygosity for these antigens are known not to affect the risk (13). The highest relative risk was found for the HLA factors. The SS and Le(a−b−) types had relative risk values around 3.5 and the lowest figure was found for factor A. Among 75 patients typed for all four marker systems the combination A/SS was found in 17 individuals, A/SS/Le(a−b−) in 5 individuals and A/SS/Le(a−b−)/HLA 13+17 in 2 individuals. The last-mentioned combination is expected to occur in the population in a frequency of 0.00015, or about 1 out of 6 700 individuals.

DISCUSSION

The HLA antigens display definite ethnic differences and in previous reports the difficulties inherent in this fact have been taken into consideration (cf. 17). In the present investigation both patients and controls were from the county of Västerbotten in northern Sweden. This is of importance, since there are distinct genetic differences between northern and southern Sweden (cf. 2).

When testing differences between patients and controls in many different parameters, as in the present study, one would expect to find associations significant at the 5% level by chance alone. Corrections such as the multiplication of P values by the number of trials will certainly reduce the risk of false-positive results, but they may on the other hand lead to the rejection of true associations. The question whether a particular association is true or false is best settled by confirmation in repeated investigations.

With these methodological considerations as a background one may conclude that there is no doubt about the increased frequencies of antigens B13 and Bw17 in psoriasis. In our study we found a significantly decreased frequency of the antigens B7 and B8. The same result has been found by most other investigators (Table V). Not all investigators have found significant differences between patients and controls, but concerning B7, all ten studies deviate in the same direction ($P<0.005$). Concerning B8, this is the case in 9 studies out of 10 ($P<0.05$). Thus it seems probable that the antigens B7 and B8 are underrepresented among the psoriatic patients. The relative risk is about 0.6–0.7.

In addition to the HLA factors B13 and Bw17, we found statistically increased frequencies of three other phenotypes in psoriasis, the SS type in the MNSs system, the Le(a−b−) type in the Lewis system and the A antigen in the ABO system. The association with the A factor was significant at the 5% level only, but the other two were highly significant ($P<0.001$). Confirmation of these results is desirable from many points of view. It would be

Table III. *Associations between markers and age at onset of psoriatic symptoms*

Marker system	Age at onset: Early (<20 years) No.	%	Late (>20 years) No.	%	P
Duffy					
Total	39		72		
a+b−	3	8	17	24	<0.05
a+b+	23	59	33	46	
a−b+	13	33	22	31	
Haptoglobin					
Total	40		72		
1-1	5	13	13	18	
2-1	12	30	32	44	
2-2	23	58	27	38	<0.05

Table IV. *Relative risks estimated on the basis of four marker systems*

Phenotype	Frequency: Controls	Patients	Relative risk
A-factor	0.490	0.582	1.5
SS	0.181	0.426	3.4
Le(a−b−)	0.117	0.323	3.6
HLA 13+17	0.015	0.172	13.6

Table V. *Frequencies of the HLA antigens B7 and B8 among psoriatic patients and controls in ten different investigations*

	B7				B8			
	Patients		Controls		Patients		Controls	
Authors	No.	%	No.	%	No.	%	No.	%
Russel et al., -72 (8)	8	18	18	20	12	14	18	20
White et al., -72 (17)	50	13	85	22	16	10	62	16
Beckman et al., -74 (3)	21	24	82	41	13	15	50	25
Schoefinius et al., -74 (9)	17	16	124	28	14	13	84	19
Schunter et al., -74 (10)	9	10	82	23	9	10	82	23
Seignalet et al., -74 (11)	7	6	41	18	13	12	36	15
Svejgaard et al., -74 (12)	20	13	602	29	21	14	497	24
Karvonen et al., -75 (4)	9	20	95	29	2	4	59	18
Krulig et al., -75 (5)	14	14	36	32	16	16	25	22
Marcusson et al., -75 (7)	7	14	29	29	9	18	16	16

of interest to ascertain whether antigens other than HLA factors contribute to the risk of developing a polygenic disease such as psoriasis. If this is the case the Ss and Lewis antigens may be involved in the etiology of other diseases too. The strengths of the associations with SS and Le(a−b−) are comparable to those previously reported for the HLA antigens B13 and Bw17.

The studies of associations with continuity of symptoms and age of onset represent an attempt to go one step further in penetrating the possible mechanisms behind the associations. Continuity of symptoms and age of onset were not found to be associated with the markers which showed strong associations with psoriasis. The previously observed association between psoriasis and the blood group factor A appears to be due entirely to the group of patients with continuous symptoms. The Fy^a factor was not associated with psoriasis *per se* but with continuous symptoms and late onset. The haptoglobin type 2-2 was overrepresented among patients showing an early onset of disease. Definite conclusions concerning the theoretical and clinical importance of these findings will of course have to await confirmatory investigations. The relative risks found for the SS and Le(a−b−) phenotypes are high enough to be of practical clinical interest, especially in combination with the HLA system.

The mechanisms behind the association with psoriasis are not known with certainty. Svejgaard and collaborators have suggested that the increase in B13, Bw17 and Bw37 in psoriasis may be secondary to a primary increase in the T7 antigen of the HLA series (13). This interpretation is consistent with the observed lack of additive effects and dosage effects for the three HLA antigens associated with psoriasis. In the five systems other than HLA, which showed statistically significant associations with psoriasis (MNSs, Le, ABO, C3 and Hp) somewhat different conditions were found. In two of these systems (Le and ABO) little or no information concerning heterozygosity is available. In the three systems where information on heterozygosity is available (Ss, C3 and Hp) the differences between patients and controls were of the same type, viz. a deficiency of heterozygotes among the patients. Thus in these three systems the differences between patients and controls with respect to gene frequencies were small or nonexistent, but significant deviations from the expected random distribution (Hardy-Weinberg equilibrium) were found. These observations can be given a common interpretation in terms of heterozygote advantage, i.e. heterozygotes are less liable to develop psoriasis.

REFERENCES

1. Baker, H. & Wilkinson, D. S.: Psoriasis. *In* Textbook of Dermatology (ed. A. Rook, D. S. Wilkinson & F. J. G. Ebling), p. 1195. Blackwell, Oxford and Melbourne, 1972.
2. Beckman, L.: A contribution to the physical anthropology and population genetics of Sweden, Variations of the ABO, Rh, MN and P blood groups. Hereditas *45* : 1, 1959.
3. Beckman, L., Brönnestam, R., Cedergren, B. & Lidén, S.: HL-A antigens, blood groups, serum groups

and red cell enzyme types in psoriasis. Hum Hered *24*: 496, 1974.
4. Karvonen, J., Tiilikainen, A. & Lassus, A.: HL-A antigens in patients with persistent palmoplantar pustulosis and pustular psoriasis. Ann Clin Res *7*: 112, 1975.
5. Krulig, L., Farber, E. M., Grumet, F. C. & Payne, R. O.: Histocompatibility (HL-A) antigens in psoriasis. Arch Dermatol *111*: 857, 1975.
6. Lomholt, G.: Psoriasis: Prevalence, Spontaneous Course and Genetics. A Census Study on the Prevalence of Skin Diseases on the Faroe Islands. G. E. C. Gad, Copenhagen, 1963.
7. Marcusson, J., Möller, E. & Thyresson, N.: HL-A antigens (17, 27, UPS) in psoriasis with special reference to patients with arthritic lesions. Acta Dermatovener (Stockholm) *55*: 297, 1975.
8. Russell, T. J., Schultes, L. M. & Kuban, D. J.: Histocompatibility (HL-A) antigens associated with psoriasis. N Engl J Med *287*: 738, 1972.
9. Schoefinius, H.-H., Braun-Falco, O., Scholz, S., Steinbauer-Rosenthal, I., Wank, R. & Albert, E. D.: Histokompatibilitätsantigene (HL-A) bei Psoriasis. Untersuchungen an 104 unverwandten Patienten. Dtsch Med Wochenschr *99*: 440, 1974.
10. Schunter, F. & Schieferstein, G.: HL-A antigene bei Psoriasis vulgaris. Hautarzt *25*: 82, 1974.
11. Seignalet, J., Clot, J., Guilhou, J. J., Duntze, F., Meynadier, J. & Robinet-Levy, M.: HL-A antigens and some immunological parameters in psoriasis. Tissue Antigens *4*: 59, 1974.
12. Svejgaard, A., Nielsen, L. Staub, Svejgaard, E., Kissmayer-Nielsen, F., Hjortshøj, A. & Zachariae, H.: HL-A in psoriasis vulgaris and in pustular psoriasis—population and family studies. Br J Dermatol *91*: 145, 1974.
13. Svejgaard, A., Hauge, M., Jersild, C., Platz, P., Ryder, L. P., Nielsen, L. Staub & Thomsen, M.: The HLA System. Karger, Basel and New York, 1975.
14. Svejgaard, A., Platz, P., Ryder, L. P., Nielsen, L. Staub & Thomsen, M.: HL-A and disease associations—a survey. Transplant Rev *22*: 3, 1975.
15. Vogel, F.: Formale Genetik des Menschen. Bedingungen und Grenzen der Erbgangsanalyse, multifaktorielle Vererbung. *In* Lehrbuch der allgemeinen Humangenetik, p. 146. Springer Verlag, Berlin, Göttingen and Heidelberg, 1961.
16. Watson, W., Cann, H. M., Farber, E. M. & Nall, M. L.: The genetics of psoriasis. Arch Dermatol *105*: 197, 1972.
17. White, S. H., Newcomer, V. D., Mickey, M. R. & Terasaki, P. I.: Disturbance of HL-A antigen frequency in psoriasis. N Engl J Med *287*: 740, 1972.

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