

PSORIASIS IN MONOZYGOTIC TWINS:
VARIATIONS IN EXPRESSION IN INDIVIDUALS
WITH IDENTICAL GENETIC CONSTITUTION

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Abstract. The variation in expression of psoriasis, in individuals with identical genetic constitutions, i.e. monozygotic twins, has been studied in a population-based sample of monozygotic twins in the Danish Twin Register. All verified and probable cases of psoriasis in twins, born between 1891 and 1930 inclusive, were ascertained. Results are presented of an examination of all members of index pairs in which both partners were alive. The zygosity determination was based in 94% of the pairs on very extensive serological examinations. Thirty-two monozygotic pairs were found to include at least one partner with unquestionable psoriasis (18 concordant, 14 discordant). The analyses give firm evidence of the contribution of genetic factors to the manifestation, age at onset, clinical type, course, and severity of psoriasis. A close association between psoriasis and HLA-B 13 and B 17 was found in both discordant and concordant pairs. No difference was found between partners from discordant MZ-pairs with regard to infections or marked 'stress' conditions.

Key words: Psoriasis; Genetics; Twin study; Heritability; HLA-typing

Family investigations of psoriasis have failed to produce convincing evidence of a simple, monogenic type of inheritance; a multifactorial origin seems more likely (1, 2, 11). In individuals with genetic susceptibility to psoriasis, the manifestation or lack of it will be due to the influence of environmental factors.

A quantitative estimate of the influence of the genetic constitution can be achieved by comparative investigations of unbiased series of monozygotic and dizygotic twin pairs, one or both partners being affected by psoriasis. In a previous study of a population-based sample of twins from the Danish Twin Register (3) it was shown that the manifesta-

tion of psoriasis depends to a large degree on the presence of the specific genotype. The age at onset, clinical type, course, and severity also seemed to be determined chiefly by the genetic constitution.

In order to obtain more detailed information about the relative importance of the genetic constitution for age at onset, morphology, course, and severity of psoriasis, intrapair comparisons and analyses of monozygotic twins have been made. This is an extension of the twin series published previously (3). Furthermore, larger twin series must be expected to throw some light on the influence of various exogenous factors, through an analysis of environmental differences between the partners in discordant monozygotic pairs, i.e. pairs in which only one partner is affected by psoriasis.

MATERIAL AND METHODS

The Danish Twin Register has been the source of the subjects for the present investigation. The construction of the Register has been described in detail previously (6). It is the purpose of this Register to follow the total population of twins, born since 1870, from birth and throughout their lives, in order to collect relevant information regarding their morbidity and mortality. The information is based on mailed questionnaires supplemented by information from hospitals, general medical practitioners, and death certificates. The collection of data is facilitated by the existence of a national personal registration system and the positive attitude of the twins. More than 90% of all twin pairs born in Denmark during the period 1870-1930 have been traced so far.

Since 1966, a question on the presence/absence of psoriasis has been included in the initial questionnaires and in the follow-up questionnaires distributed to all twins at intervals as long as they are alive.

In the present study, all twins in the Register, who in their reply to the questionnaire had indicated presence of

psoriasis were picked out. The investigation reported here includes only same-sexed pairs, born in the period 1891–1930, with both partners still alive at the time of examination, and who were classified as probably monozygotic (MZ) based on questions about the degree of similarity between the partners, as described previously (6), or on extensive serological tests.

A total of 54 twins, originating from 47 pairs, fulfilled the criteria given above. An attempt was made to visit all 94 individuals. One pair was excluded as the proband had died shortly before the examination, and the co-twin refused examination. Another proband died shortly before the examination, but was included as detailed hospital records were available, and the co-twin agreed to be examined. In the remaining 45 pairs only one proband and one partner refused to meet the examiner (F. B.), but an interview by telephone was permitted and supplemented with information from dermatologists consulted previously.

A full medical history was obtained. If psoriasis was actually or had previously been present, the age at onset, morphology, distribution, course, and precipitating factors (if any) were recorded. A clinical examination was performed, and information on psoriasis in all first-degree relatives collected. A blood sample was taken for the determination of zygosity.

Clinical diagnosis

The diagnosis of psoriasis was established when sharply demarcated, infiltrated, red, papular elements with characteristic scales, or eventually, a Bulkley membrane and Auspitz sign were found at the examination. If the skin was clear at the actual examination, the diagnosis had to be based on anamnestic data, possibly supplemented by information from general practitioners or dermatologists consulted during previous attacks. If no other area than the scalp was involved, the scalp lesions had to be typical before the diagnosis of psoriasis was accepted. Flexural psoriasis was only considered as fulfilling the present criteria if psoriatic lesions had been observed previously on sites of predilection, or if the condition, flexural psoriasis, had been diagnosed by a dermatologist.

Pustular eruptions of palm and/or soles were classified neutrally as palmo-plantar pustulosis unless psoriatic lesions were found elsewhere at the clinical examination or were recorded anamnestically. The last-mentioned cases were recorded as localized pustular psoriasis and included in the calculations as psoriasis.

Nail lesions alone were not accepted as sufficient for the diagnosis psoriasis.

Course and severity

The clinical course was rated in four main categories in much the same way as used by Lomholt (8) in cases with a duration of more than 4 years:

LR: light, recurring eruptions mainly on elbows and knees or on the scalp, but no symptoms for longer periods.

LC: light but fairly constant symptoms, mainly on elbows, knees or scalp, but not really disabling the patient.

MC: Moderate, almost constant, sometimes even

severe symptoms, also on the trunk, but with minor spreading.

SC: Severe, constant eruptions affecting the limbs, large parts of the trunk, and occasionally also the face and backs of the hands.

Those patients who had had severe eruptions at an early age, but much milder symptoms later on, have been given the additional symbol ES.

Zygosity diagnosis

The zygosity diagnosis was based on red cell, serum and enzyme group determinations (a total of 15 systems), supplemented by HLA typing in most cases. Complete serological similarity was accepted as evidence of monozygosity, since this assumption under the present conditions has a probability of more than 99%. In cases where blood samples were not available, the principles for clinical zygosity diagnosis used by the Danish Twin Register (6) were applied.

RESULTS

Examination of the 53 index cases, originating from 46 pairs, revealed that 14 of these did not fulfil the diagnostic criteria. Diagnoses based on anamnestic information and the actual clinical examination were: seborrhoeic dermatitis (4), palmoplantar pustulosis (2), hand eczema (2), atopic dermatitis, stasis eczema, psoriatic nail changes, necrobiosis lipoidica and xeroderma. In one case the twin had by sheer mistake indicated presence of psoriasis in the questionnaire. Thus 39 twins from 33 MZ pairs were left with a well-established diagnosis of psoriasis.

The zygosity diagnosis in these 33 pairs was based on serological examination in 31 pairs and clinical examination in 2 pairs. The serological tests disclosed one pair to be DZ, and this pair was consequently excluded from the present study. The remaining 32 MZ pairs (20 females, 12 males) where one or both partners had psoriasis form the basis for the following calculations. A survey of the data is given in the Appendix. Fourteen of these pairs (8 females, 6 males) were included in the twin series published previously (3). The sex distribution in the present sample is consistent with the total sample of twin pairs in which both partners were alive.

The pairwise concordance rate, which gives the number of pairs in which both partners have psoriasis out of the total number in the group, was equal to 0.56 (18/32) in the MZ group male pairs 0.75 (9/12), female pairs 0.45 (9/20). This difference is not statistically significant ($p > 0.10$; Fisher's exact test).

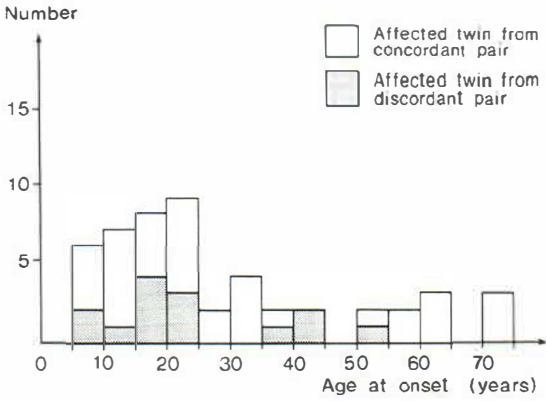


Fig. 1. Age at onset of psoriasis in 50 affected twins.

The probandwise concordance rate gives the proportion of independently ascertained probands who have a similarly affected partner. 38 MZ probands were ascertained independently and 24 of these had a psoriatic co-twin; thus, the probandwise concordance rate was 0.63 (24/38) in MZ twins; males 0.8 (12/15) females 0.5 (12/23). This implies that individuals with a MZ psoriatic twin partner has a risk around 65% (provided they live long enough) of developing this affection. Median age at examination in the present study was 64 years (range 50–83 years).

Based on a probandwise concordance rate of 0.63 in MZ twins found in this study and a population frequency of psoriasis at 3% (4), heritability is found to be $91 \pm 11\%$ (1 SE) according to the method published by Smith (9).

Age at onset

Fig. 1 gives the age at manifestation of all affected individuals. The median age at manifestation was 20.5 years. The median age at manifestation in twins from concordant pairs was 24 years and from discordant pairs 19 years. This difference is not statistically significant ($p > 0.1$; Mann-Whitney rank sum test for un-paired data); in concordant pairs one partner was selected by randomization.

The age at onset was identical in the two partners in three concordant pairs, and the interval between the ages at onset was 1–5 years in 7 pairs, 6–15 years in 5 pairs and 16, 25 and 46 years respectively in the remaining 3 concordant MZ pairs.

Course and severity

The distribution of course and severity is shown in Fig. 2. Close to 75% were types with rather light

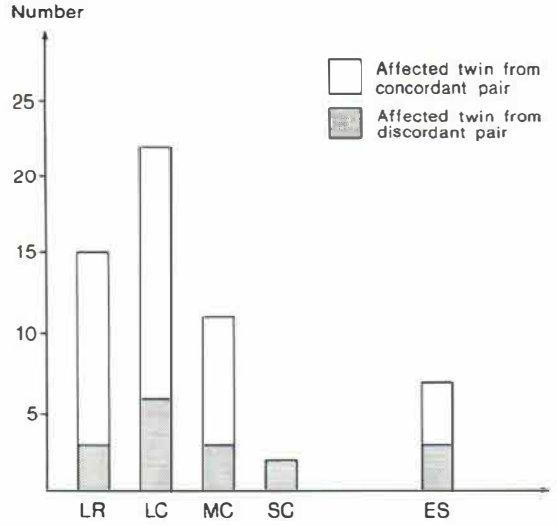


Fig. 2. Course and severity of psoriasis in 50 affected twins (duration of psoriasis >4 years). LR: light, recurring eruptions; LC: light, constant symptoms; MC: moderate, almost constant symptoms; SC: severe, constant symptoms; ES: severe eruptions early, milder symptoms later.

symptoms (LR+LC) and the distribution among twins from concordant and discordant pairs was quite similar, but it is noteworthy that the most severe cases were seen in two discordant pairs.

As seen from Fig. 3 course and severity was identical in 12 of 18 concordant pairs. The frequency of identical course and severity observed in partners from concordant pairs is higher than expected ($p < 0.01$; χ^2 -test).

Morphology

The morphology of the eruptions was registered as psoriasis en plaques (pl), guttate/nummular eruptions (gt/nm), localized pustular psoriasis of palms and/or soles (pp) and inverse psoriasis (pi). The morphology of the eruptions was the same in 13 of 18 concordant pairs. In the remaining 5 pairs the differences were pl. versus pl/nm in 4 pairs and pl. versus gt/nm in 1 pair. The frequency of identical morphology observed in concordant pairs is higher than expected ($p < 0.001$; χ^2 -test). In 10 concordant pairs morphology, course and severity were identical in the partners.

Relation to arthritis

Special attention was paid to all possible signs of arthritis. This diagnosis was based on the interview,

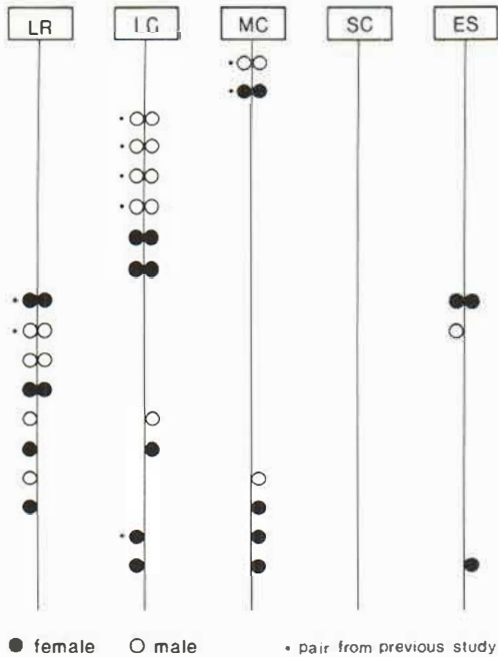


Fig. 3. Intrapair comparison of course and severity in 18 monozygotic pairs showing concordance with respect to psoriasis (duration of affection >4 years). See caption to Fig. 2 for explanation of other abbreviations. Black dot: included in previous study (3).

the examination and information from hospital records concerning diagnosis, roentgenological findings and serological tests. Five cases of arthritis were found in four pairs. Arthritis was found concordant in one pair which was also concordant with respect to psoriasis of LR-type and to age at onset. In one pair of concordant psoriasis, arthritis was present discordant affecting only the twin with early age at onset and more severe course of psoriasis than the co-twin. In one pair of discordant psoriasis the psoriatic twin (SC-type) was affected by seronegative arthritis whereas the co-twin was completely unaffected. In one pair of discordant psoriasis the non-psoriatic twin had recurrent palmo-plantar pustulosis and severe, seropositive arthritis.

Relation to localized pustular psoriasis and palmo-plantar pustulosis

In 3 female pairs pustular eruptions of palms and/or soles had been present together with affections of typical psoriasis in other skin areas. These pairs were discordant and the co-twins were unaffected

by psoriasis or palmo-plantar pustulosis. Pustular eruptions of palms or soles had not been present in concordant pairs.

HLA-type

HLA-typing was performed in at least one partner from all pairs (see key to appendix for further details). In pairs where HLA-typing was performed in only one partner, the type was registered concordant, as the zygosity diagnosis had been established before by extensive serological tests. HLA-type B 13 was present in 4 pairs (3 conc. and 1 disc.) and type B 17 in 12 pairs (5 conc. and 7 disc.) thus confirming the association between these two antigens and psoriasis. HLA-B 13 and/or B 17 was present in 7/18 concordant pairs and 8/14 discordant pairs; this difference is not statistically significant. In 4 pairs affected by arthritis, HLA B 13 or B 17 were not present. In 3 pairs affected by localized pustular psoriasis, HLA B 17 was present in all pairs.

Exogenous influences on manifestation of psoriasis

A search for possible exogenous influences of major importance in the development of psoriasis was made during the interviews. Special attention was paid to marked 'stress' based on personal, familial and occupational circumstances, judging by the investigator's general impression, and to infections, especially those often caused by streptococci.

No differences in 'stress' conditions or recurrent infections were seen between affected and non-affected partners from discordant pairs, when comparisons are performed in pairs where only one partner was exposed to the factor in question.

Neither marital status, social status, nor occupation seemed to have any relation to the presence of psoriasis in discordant pairs.

MZ pairs concordant with respect to psoriasis had lived together for 24 years on average (median value, range 14-65) and discordant pairs had lived together for 19 years (range 15-38). This difference is not statistically significant ($p > 0.1$; Mann-Whitney rank sum test for un-paired data).

DISCUSSION

The present material was drawn from a population sample and not from dermatological clinics. Among 50 affected MZ twins, 33 cases were verified at the

clinical examination and in only 17 cases had the diagnosis to be based on anamnestic information, but in 14 cases this could be supported by diagnosis given by dermatologists (10 cases) or general practitioners (4 cases) consulted previously.

All twins studied had passed the age of 50, so very few additional pairs may be expected to transfer from the discordant to the concordant group. The zygoty diagnosis was verified in nearly all cases by very extensive serological tests, which is contrary to most other twin samples published previously.

The pairwise and probandwise concordance rate in this sample agrees with the concordance rates in the sample published previously (3).

By using the classical twin method the strong influence of genetic factors on the manifestation of psoriasis was demonstrated in the first study (3); the heritability was estimated to be about 90%. This high heritability estimate is supported by identical results in the present sample. Furthermore, Ananthakrishnan et al. (2), found by analogous methods, on the basis of Lomholt's family material from the Faroe Islands, that the heritability was 91% when all first-degree relatives were combined. A heritability of 90% implies that the variation observed between individuals with respect to presence or absence of psoriasis is due almost entirely to their gene differences and only to a limited extent to differences in the environment which they experience at home or at work.

Ananthakrishnan et al. (1), based on Hellgren's data (7), and Watson et al. (11) found a heritability of about 65%. The higher heritability estimate found in the present study could be due partly to the higher mean age of the probands, the longer observation period and a high diagnostic certainty based on the personal examination.

Collections of casuistic reports from dermatologic clinics are unreliable as a basis for an estimate of the importance of heredity, as there is a tendency to acquire an overrepresentation of concordant MZ twins with early age at onset, since twin status is more likely to be recognized when both individuals manifest the trait at a younger age. Farber et al. (5) collected 39 MZ pairs from the literature; when combined they yield a pairwise concordance rate of 26/39 (67%), which is higher than that found in the present study. This might be partly due to the above-mentioned bias. Farber et al. (5) collected their own large series of twins

through inquiries to dermatologists all over the United States: the information was gathered almost exclusively by questionnaire. The study included 30/41 (73%) concordant MZ pairs and 11/41 (27%) discordant MZ pairs. The median age at examination in the whole sample (MZ + DZ pairs) was 16.7 years, which is much lower than in the present study. Similarly, the median age at onset, 14 years, was lower when compared with the present study. In spite of the low age at examination a surprisingly high concordance rate was found, which may be due to the bias inherent in their sampling procedure, as discussed by the authors (5).

The present study shows that environment may only to a limited extent modify age at onset, course, and severity. The great influence of genetic factors on course and severity is apparent from the observation that only six of eighteen concordant MZ pairs showed some major difference in these respects. Morphology and age at onset were also much alike in MZ twins, confirming the observation made by Farber et al. (5). This close concordance may have been influenced by a greater similarity of environmental conditions in MZ twins than in ordinary siblings. There was a slight, but statistically insignificant, tendency in MZ pairs to have lived together for a longer time if they were concordant with respect to psoriasis rather than discordant. Differences in the main morphological features were found in only a few concordant pairs. Thus, in one of the concordant pairs, typical plaque psoriasis of MC-type had been present in one twin from the age of 16; at the age of 31, minor plaques developed at sites of predilection in the co-twin, but flexural psoriasis and keratotic hand eczema were the main features.

In four of fourteen discordant MZ pairs the non-affected partner had skin symptoms which could possibly be a manifestation of the psoriatic trait. In these non-affected partners pitting and distal onycholysis were found in some fingernails in 2 cases, and in the 2 remaining partners, keratotic hand eczema and palmo-plantar pustulosis respectively. However, these cases failed to fulfil the strict diagnostic criteria of the present study and were classified as discordant because the co-twin had typical psoriasis vulgaris, though it may still remain an open question whether they are aetiologically related to psoriasis.

Localized pustular psoriasis on the palms or soles

had been present in the psoriatic partner from three discordant female pairs, whereas such eruptions had not been present in concordant pairs. One discordant MZ pair included one partner with light psoriasis vulgaris and one partner with persistent palmo-plantar pustulosis and arthritis. However, more similar cases are needed to clarify if these pustular eruptions and psoriasis vulgaris have a common aetiological background.

The analyses of the distribution of HLA types confirmed the well known association with antigens B 13 and B 17 of the B locus (10), but it was also apparent that psoriasis could develop even when neither of these antigens is present. HLA B 13 and/or B 17 was present more frequently in discordant than in concordant pairs, but this difference is not statistically significant. This might perhaps be indicative of genetic heterogeneity in the two groups. However, the distribution according to course and severity is the same in concordant and discordant pairs, which speaks against a hypothesis of genetic heterogeneity. Further analyses of the twins based on information about psoriasis in first-degree relatives are in progress to elucidate whether genetic heterogeneity might account for this observation. Recently a strong association with HLA-Cw6 has been shown (10). In the present investigation there has not been tested for the presence of the HLA-Cw6 antigen because of lack of testsera during the 5 years in which the HLA typing was performed.

The search for environmental factors that could have influenced the development of psoriasis in discordant MZ pairs was so far unsuccessful. Neither infections, nor conditions that might have caused stress or conflicts were observed more often in the affected than in the non-affected member of discordant pairs.

It does not seem likely that the classical twin studies could contribute very much more to the elucidation of the aetiology of psoriasis vulgaris. However, comparative pathophysiological investigations of partners from discordant MZ pairs may be of great interest, as the non-affected partner is an individual with a certain predisposition to psoriasis.

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APPENDIX

Survey of probands and their partners from monozygotic pairs, where both twins were alive

I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
*9017 f	1891	+	P	w	p	24	MC	pl+gt/nm	A+f	A (cr)+	A 2, 11; B 15
*3424 f	1901	+	P	w	p	70	LC	pl	A+d		
*6039 m	1901	+	P	w	p	16	MC	pl+pi	A+h		A 1, 2; B 8
3615 f	1901	+	P	w	p	31	MC	pl+pi	A+h		
12323 f	1901	+	P	w	p	6	LC	pl	A+h		A 1, 9; B 7, 13
10845 f	1905	+	P	m	p	7	LC	pl	A+h		
*2620 f	1905	+	P	m	p	70	LC	pl+gt/nm	B+d		A 2, 9; Bw 44 (12)
*6411 m	1906	+	P	d	p	71	LC	pl+gt/nm	A		
*3699 f	1906	+	P	m	p+pp	20	MC	pl+pp+pi	C+h		A 2, 26; B 17, w 38 (w 16)
*3714 f	1907	+	P	m	p	10	LC/ES	pl+gt/nm	A+d		A 2, 26; B 17,40;Cw 3
1969 m	1907	+	P	m	p	17	LR	pl+gt/nm	B+f		A 2; B 7
*6442 m	1907	+	P	m	op	67			A+h	A (cr)+	
*11040 m	1907	+	P	m	p	50	LC	pl	A+f		A 1, 2; B 8, 27
*53425 m	1907	+	P	m	p	64	LC	pl	A		
52036 f	1908	+	P	d	p+pp	50	LC	pi+pp	A+d		A 3, 28; B 17, 35
*50630 m	1910	+	P	m	p	33	LR/ES	gt	B+d		A 1, 28; B 13, 17
52340 f	1910	+	P	m	p	25	LR/ES	gt/nm	B+h		
*53101 f	1910	+	P	m	p	8	LC	pl	A+d		A 2; B 17, 18
*50337 f	1910	+	P	m	p	24	LR	pl	B		
*51350 f	1910	+	P	d	p	20	MC	pl+nm	A+h		A 2, 3; B 15, 27
53959 m	1910	+	P	u	p	20	MC	pl+nm	A+h		
51334 f	1910	+	P	u	p	18	LC	pl	B+f		A 2; B 15, 17
60305 f	1911	+	P	u	p	19	LC	pl	A+f		
64009 f	1911	+	P	m	p	14	LC	pl	A+d		A 1, 2; B 8, 13
60281 m	1911	+	P	m	p	14	LC	pl+gt/nm	C+h		
60302 f	1911	+	P	d	p	35	LC	pl	A		A 3; B 7, 27; Cw 2
60956 f	1913	+	P	m	p	8	LR/ES	gt/nm	B+h		A 9; B 15
60345 m	1913	+	P	m	p	14	LR	pl	B+f		
60931 f	1913	+	P	w	p	60	LR	pl+pi	B+d	A (c)	A 3, 11; B 7, w 35;
	1914	+	P	m	p	57	LR	pl+pi	A+d	A (c)	Cw 4
	1914	+	P	m	p	20	LC	pl	A+f		A 1; B 8, 13
	1917	+	P	w	p+pp	40	LC	pl+pp	B+d		A 1, 2; B 7
	1917	+	P	m	p	8	LC	pl	A+d		A 25 (10), 29 (w 19); B 18, 12
	1918	+	P	m	p	30	MC	pl+gt/nm	A+f		A 1, 2; B 8, w 50 (w 21)
	1920	+	P	m	p	32	LR	pl	B		
	1920	+	P	m	p	6	MC+ES	pl+gt/nm	A+h		A 2, 9; B 5, 17; Cw 3
	1920	+	P	m	p	57	LR	pl	A+f		A 1, 2; B 7
	1920	+	P	m	p	60	LR	pl	A		
	1925	+	P	m	p	10	LC	pl	B+d		A 1, 11; B 15, 37
	1925	+	P	u	p	10	LR	pl	B		
	1925	+	P	u	p	42	SC	pl+gt/nm	A+h	A (cr=)	A 2, 3; B 15, 27
	1926	+	P	m	p	16	LC	pl+gt/nm	A		A 2; B 7, 17
	1926	+	P	m	p	27	LC	pl+gt/nm	A		
	1927	+	P	u	p	16	LR	pl+gt/nm	B+f		A 2, 3; B 7, 8
	1927	+	P	m	p	15	SC	pl+gt/nm	A+h		A 1, 9; B 7, 18
	1928	+	P	m	p	21					
	1928	+	P	u	p	18	LR	pl	B+d		A 2; B 8, 17
	1928	+	P	u	p	39	MC	pl+gt/nm	A+h		A 1; B 17
	1929	+	P	u	p	14	LR	pl	A		
	1929	+	P	m	p	24	MC+ES	pl+gt/nm	A+h		A 2, w 32; B 17, 40
	1929	+	P	m	p	21	MC+ES	pl+gt/nm+pi	A+d		A 3, 9; Bw 35, w 47;
	1929	+	P	m	p	24	LC	pl+nm+pi	A+d		Cw 4

Key to Appendix

I: Serial no. of the pair in the Danish Twin Register; each of the partners is given one line. m=male, f=female, asterisk=pair from previous study.

II: Year of birth.

III: +=register proband, i.e. psoriasis present according to questionnaire.

IV: P=proband according to criteria of present study.

V: marital status: d=divorced, m=married, u=unmarried, w=widow, widower.

VI: Final diagnosis: p=psoriasis vulgaris, pp=localized pustular psoriasis of palms and soles, op=pustulosis palmaris et plantaris only, 0=no present or previous signs or symptoms of psoriasis.

VII: Age at onset as stated during medical examination.

VIII: Course LR=light, recurring eruptions, LC=light, constant eruptions, MC=moderate, constant eruptions, SC=severe, almost constant eruptions, ES=severe eruptions at an early age. See text for further explanations.

IX: Morphology pl=psoriasis en plaques, gt/nm=guttate/nummulate eruptions at some time, pp=localized pustular psoriasis of palms and/or soles at some time, op=palmo-plantar pustulosis at some time, pi=inverse psoriasis=flexural psoriasis.

X: Verification of diagnosis: A=anamnestic and clinical symptoms at examination, B=anamnestic information, no symptoms at examination, C=anamnestic information only, no examination performed, f=diagnosed by family doctor, d=diagnosed by a practising dermatologist, h=diagnosed at a department of dermatology.

XI: A(c)=clinical diagnosis of arthritis; A(cr)=clinical and radiological diagnosis of arthritis; appended plus or minus sign indicates result or rheumatests.

XII: HLA-phenotypes. The HLA-typing was done by a standard lymphocytotoxicity micromethod, using a large number of antisera, thus allowing the possible identification of the utmost majority of the known HLA-A, B, and some C antigens.