Psoriasis in First-degree Relatives of Psoriatic Twins

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Analysis of the presence of psoriasis in all first-degree relatives of psoriatic twin probands, 38 monozygotic (MZ) and 24 dizygotic (DZ), has been performed in order to clarify if genetic heterogeneity might be present (the twin-family method). The probands were derived from a population based sample of like-sexed twin pairs. An almost identical frequency of psoriasis in parents, siblings and children, with no sex diffrence, was found. By comparisons of empirical risk figures for psoriasis in first-degree relatives of (*a*) concordant as compared with discordant MZ probands and (*b*) HLA-B 13 and/or HLA-B 17 positive MZ probands compared with MZ probands lacking these antigens, no clue to the presence of genetic heterogeneity was found. An almost identical risk in co-twins and ordinary siblings of DZ-probands was found. The data were incompatible with autosomal recessive or X-linked inheritance, but not incompatible with autosomal dominant inheritance with reduced penetrance or with multifactorial inheritance. *Key words: Psoriasis; Genetics; Twin study; Twin-family method; HLA-typing.* (Received July 6, 1983.)

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The relative importance of genetic factors in the origin, age at onset, clinical type, course and severity of psoriasis has been studied recently by the author on the basis of a population-based twin sample, 14 monozygotic (MZ) and 22 dizygotic (DZ) like-sexed pairs, from the Danish Twin Register (1). Furthermore, the variation in expression of psoriasis in individuals with identical genetic constitution has been studied in an extended series of 38 MZ probands originating from 32 MZ pairs (18 concordant, 14 discordant) extracted from the same twin-register (2). The analyses gave firm evidence of the contribution of genetic factors to the manifestation, age at onset, clinical type, course, and severity of psoriasis. Analysis of the distribution of the HLA types B 13 and B 17, showed that these antigens were present slightly more frequently in discordant than in concordant pairs, which is contrary to what might be expected, as concordance is more likely to occur in pairs with high genetic liability to psoriasis. This might be indicative of genetic heterogeneity in the two groups, even though this difference was statistically insignificant. However, the distribution according to course and severity was the same in twins from concordant and discordant pairs (2), which gives no support to a hypothesis of genetic heterogeneity. In the present study, further analyses of this twin-material, based on information about psoriasis in first-degree relatives (the twin-family method) (3) has been performed to elucidate whether genetic heterogeneity might be present.

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 (4, 5). It is the purpose of this nation-wide Register to follow the total population of twins, born since 1870, from birth and throughout their lives, in order to collect relevant information regarding morbidity and mortality. The

primary information is based on birth registries and mailed questionnaires supplemented by information from hospital records, general medical practitioners, and death certificates. More than 90 % of all twins from like-sexed twin pairs born in Denmark during the period 1870--1930 have been traced so far (5).

Since 1966, a question concerning presence/absence of psoriasis has been included in the initial questionnaires and in the follow-up questionnaires distributed to twins still 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. Included in this study were twins from like-sexed pairs, born in the period 1891–1920 (DZ-pairs) and 1891–1930 (MZ-pairs), with both partners still alive at the start of the study. All twins who had indicated presence of psoriasis were examined by the author and the diagnosis of past or present psoriasis was established or rejected according to clinical criteria described previously (1, 2).

Included as probands were twins from like-sexed pairs born in the period 1891–1920 (DZ-pairs) and 1891–1930 (MZ-pairs) who (*a*) had indicated presence of psoriasis at the mailed questionnaire, (*b*) were alive at the time of examination, and (*c*) fulfilled the criteria for the diagnosis of past or present psoriasis at the examination.

The twin partners of probands were examined in the same way, and the diagnosis of psoriasis, if present, was established according to the same criteria.

The zygosity diagnosis was based on red cell, serum and enzyme group determinations supplemented by HLA typing in most cases including all MZ-pairs. The HLA typing was done by a standard lymphocytotoxicity micromethod, using a large number of antisera, thus allowing the possible identification of the majority of the known HLA-A, B and some C antigens. Complete serological similarity was accepted as evidence of monozygosity, since this assumption under the present conditions has a probability of more than 99.0%. In four cases where blood samples were not available, the principles for clinical zygosity diagnosis used by the Danish Twin Register (4) were applied.

Sex, year of birth and year of death of deceased persons, in parents, siblings and children, were recorded during the interview with the probands and partners, and information on past or present psoriasis in these first-degree relatives was recorded according to the information given by the twins.

The MZ series (2) comprises 38 MZ probands originating from 32 MZ pairs. The DZ series (1) has been supplemented by one proband from one pair which was transferred from the MZ category after serological zygosity determination. Thus, the DZ series comprises 24 DZ probands from 23 pairs. Median age at examination was 64 years (range 50-83) in the MZ twin series and 64 years (range 55–77) in the DZ series.

Statistical methods

In the following calculations probandwise counting (where relatives of doubly ascertained twin pairs are counted twice) has been used, as recommended by Rice et al. (6). The significance tests have been based on χ^2-test, Mann-Whitney test, Fisher's exact test and Mantel-Haenszel test (7). The level of significance is 5 %. The risk of manifestation of psoriasis in first-degree relatives of probands from concordant versus discordant pairs has been analysed by comparing the odds ratio (OR) for the two groups. Odds ratio = the cross-product ratio from a 2×2 contingency table. 95 % confidence limits were calculated according to Miettinen (8).

RESULTS

In Table I psoriasis in first-degree relatives of MZ probands by sex and HLA type of probands, are given. Information concerning one pair of parents and one father in the MZ series was not available, as these parents were unknown to the probands due do adoption or birth out of wedlock. HLA + or − indicates presence or absence of HLA B 13 and/or B 17 at HLA typing. The proportion of actual or previous psoriasis in psoriatic relatives of MZ probands are: *Parents:* 11/73 (15 %). Parents related to probands from concordant pairs: 7/48 (15%) and from discordant pairs 4/25 (16%). *Siblings:* 27/135 (20%). Siblings related to probands from concordant pairs 24/108 (22%) and from discordant pairs 3/27 (11%). *Children:* 6/63 (10%). Children of probands from concordant pairs 2/34 (6%) and from discordant pairs 4/29 (14%). None of the differences between the groups compared are statistically significant.

The median age of siblings of MZ probands from concordant pairs was 67 years (range 24–88) and from discordant pairs 56 years (range 11–77). Similarly, the median age of the children was 32.5 years (range 14–54) versus 32 years (range 13–46). These differences are not statistically significant (Mann-Whitney test).

The risk of manifestation of psoriasis in first-degree relatives of probands from concordant versus discordant pairs has been analysed by comparing the odds ratio (OR) for the two groups. *Parents:* OR=0.90 (0.24–3.41), *siblings:* OR=2.29 (0.65–8.02), *children:* OR=0.39 (0.07–2.20). These differences between the groups are not statistically significant (χ^2-test).

The risk of manifestation of psoriasis in first-degree relatives of MZ probands with or without HLA B 13 and/or B 17 has been analysed similarly by comparing the odds ratio for the two groups. *Parents:* OR=0.94 (0.25–3.57), siblings: OR=2.52 (0.70–9.06), children: OR=0.56 (0.10–3.06). These differences between the groups are not statistically significant (Mantel-Haenszel test).

In Table II psoriasis in first-degree relatives of DZ probands, divided by sex and relation to probands from concordant versus discordant pairs, are given. One father in the DZ series was unknown. The proportion of actual or previous psoriasis in relatives of DZ probands are: *parents:* 11/47 (23%), *siblings:* 9/90 (10%), *children:* 3/48 (6%).

The odds ratio for manifestation of psoriasis, in first-degree relatives of DZ probands from concordant versus discordant pairs, are: *parents:* OR=2.33 (0.47–11.51), *siblings:* OR=0.00, *children:* OR=4.00 (0.36–44.59). These differences are statistically significant only in the group of siblings (Fisher's exact test).

Table I. *Presence of psoriasis in first-degree relatives of monozygotic (MZ) probands from concordant and discordant pairs by sex and HLA-B types in probands*

Key to abbreviations: psoriasis (P) present (+) or absent (−). HLA +/− indicates presence/absence of HLA-B 13 and/or B 17 in probands. Male probands (M), female probands (F)

MZ-probands	Sex			Father	Mother	Sister	Brother	Daughter	Son	Total
Concordant	M	HLA+	P+	3	0	2	7	2	0	14
	M	HLA+	P−	3	6	8	18	6	2	43
	M	HLA−	P+	1	0	1	6	0	0	8
	M	HLA−	P−	5	6	11	11	5	2	40
	F	HLA+	P+	1	0	1	1	0	0	3
	F	HLA+	P−	3	4	3	0	0	3	13
	F	HLA−	P+	2	0	2	4	0	0	8
	F	HLA−	P−	6	8	14	19	4	10	61
Total				24	24	42	66	17	17	190
Discordant	M	HLA+	P+	1	0	0	0	1	0	2
	M	HLA+	P−	0	1	3	1	2	0	7
	M	HLA−	P+	0	0	0	0	0	0	0
	M	HLA−	P−	2	2	5	1	2	2	14
	F[a]	HLA+	P+	1	0	1	1	1	1	5
	F	HLA+	P−	4	6	3	6	6	7	32
	F	HLA−	P+	2	0	0	1	0	1	4
	F	HLA−	P−	2	4	4	1	3	3	17
Total				12	13	16	11	15	14	81

[a] One pair of parents and one mother unknown.

DISCUSSION

The diagnosis of psoriasis in the probands was established with high diagnostic certainty according to clinical criteria based on anamnestic information and personal examination. On the other hand, information on psoriasis in all first-degree relatives was based on anamnestic information from the twins, collected during the interview, and thus established with less diagnostic certainty. In a population-based sample it was estimated that 20% of positive answers on questions about psoriasis were false-positives (9). However, in the present investigation on psoriasis among first-degree relatives, the information is estimated to be slightly more valid as it is collected by interview from both twins—one or both familiar with the disease by personal experience.

In some previous studies of series of psoriatic probands from dermatological clinics mainly, "familial occurrence" was recorded, as tabulated by Farber et al. (10), varying from 4–90%. These studies are not open for comparisons due to lack of statement of age-structure, differences in selection of probands or differences in the groups of relatives included. Farber et al. (10) in a questionnaire survey of 5 600 psoriatics (The Stanford Psoriasis Life Histories Survey) found that 47% of siblings plus parents were reported to suffer from actual or previous psoriasis. This prevalence rate is remarkably higher than 11% (parents 14%, siblings 9%) found in a preceding study from Stanford (11) based on information from 698 psoriatics, collected from dermatological clinics in the same way. These differences cannot be explained by differences in age-structure, as the mean age of the psoriatics given the questionnaire was about 40 years in both studies. The rates given in the last mentioned study (11) are in agreement with those (parents 18%, siblings 16%) found in the present study, as the slightly higher prevalence may be due to the higher median-age of the probands in the present study.

Lomholt (12) in his census study from the Faroe Islands found a prevalence of actual or previous psoriasis at 16–19% in the total group of parents, siblings and children over 20 years of age, with minimal differences between the groups, which is in agreement with the present study. Hellgren (13) in a population-based sample found an overall frequency at 8% of psoriasis in first-degree relatives (parents 12%, siblings 9%, children 5%). This overall frequency is less than 15% found in first-degree relatives of MZ + DZ probands in

Table II. *Presence of psoriasis in first-degree relatives of dizygotic (DZ) probands from concordant and discordant pairs in relation to sex of probands*

Key to abbreviations: Psoriasis (P) present (+) or absent (−). Male probands (M), female probands (F)

DZ-probands	Sex		Father	Mother	Sister	Brother	Daughter	Son	Total
Concordant	M	P+	0	1	0	0	0	0	1
	M	P−	2	1	9	8	2	1	23
	F	P+	2	0	0	0	1	0	3
	F	P−	0	2	10	0	1	1	14
Total			4	4	19	8	4	2	41
Discordant	M	P+	3	2	3	2	0	0	10
	M	P−	4	5	7	14	7	8	45
	F[a]	P+	1	2	2	2	0	2	9
	F	P−	11	11	17	16	16	9	80
Total			19	20	29	34	23	19	144

[a] One father unknown.

the present study, which may be partly due to the lower median-age, about 40 years, of the probands in the Swedish study.

In the present study a slightly lower frequency of psoriasis was found in the group of children (8%) compared with siblings (16%) and parents (18%), which may be due to the lower median age of the children.

The fact that some of the MZ twins (2) are concordant and others discordant for psoriasis may be caused by one or both of two reasons: (*a*) manifestation of psoriasis may be influenced by nongenetic factors and (*b*) there may be two different types—an inherited and a noninherited form. These possible explanations may be separated by comparing empirical risk figures for psoriasis in close relatives of concordant as compared with discordant MZ pairs (3). If there is heterogeneity and one type of psoriasis is nongenetic, the risk of relatives of discordant MZ pairs will be no higher than in the general population, while discordance caused by non-genetic factors will lead to similar risks among relatives of concordant and discordant twins. In the present investigation the overall risk of first-degree relatives of concordant versus discordant MZ probands was calculated at 17% and 14% respectively; this difference is not statistically significant. Furthermore, the risk of relatives of discordant MZ probands is far higher than the risk of about 3% (9) in the general population. Thus, no clue to the presence of genetic heterogeneity was found, and discordance in MZ pairs must be due to differences in non-genetical environmental factors.

DZ-twins are no more similar genetically than other siblings, but are supposed to be exposed to more identical postnatal environmental factors than ordinary siblings. Thus, concordance of psoriasis in DZ pairs might be due to the similarity in environmental factors, if these factors are of major importance in psoriasis, and in this case a higher risk of psoriasis might be expected in the partners of DZ probands than in ordinary siblings. Contrary, if genetical factors are of major importance identical risk must be expected for the DZ co-twin and ordinary siblings. In the present investigation the risk of psoriasis in siblings of DZ-twin probands was calculated at 10%, which is in agreement with the risk of around 15% in individuals who have a DZ-twin partner with psoriasis (1). Thus, a further support to the major importance of genetical factors has been found.

Since the first publications (14, 15) several authors, including Scandinavian investigators (16, 17, 18), have confirmed the association between psoriasis and HLA B 13 and B 17. Later on, an even stronger association with HLA-Cw6 (19, 20) has been demonstrated. In the present series of MZ probands testing for the presence of HLA-Cw6 was not performed because of lack of testsera during the time of investigation. In the series of MZ probands (2) the association between psoriasis and HLA B 13 and B 17 was confirmed. By application of the twin-family method to the present data, similar risks in first-degree relatives of those probands with and those without HLA B 13 and/or B 17 were found. Thus, no support appeared for the presence of two genetically different types of psoriasis related to presence or absence of the HLA-types mentioned, which is in accordance with our previous study (2).

In some studies a higher incidence of a positive "family history" in HLA B 13 and/or B 17 positive patients than in patients lacking these antigens, has been found (15, 16, 21). In a more detailed study by Svejgaard et al. (22) it appeared that the frequency of affected relatives was more than twice as high in siblings and children of probands carrying one of the psoriasis-associated HLA-B antigens compared to the corresponding frequency for probands lacking these antigens. These findings disagree with the present results, where no significant differences were found. However, mutual comparisons between these prevalence-based case-referent studies and the present series are doubtful, mainly due to lack of information on the age structure of the study populations (23). Furthermore,

differences between a population-based sample as the present series and samples derived from hospital files might exist.

Theoretically, the association of psoriasis with some HLA-antigens may be due to linkage disequilibrium between these antigens and genes of major importance for the development of psoriasis, or these HLA-antigens might be of more specific immunological importance in the pathogenesis. In the first case similar risk of psoriasis in relatives of probands with or without these HLA-antigens might be expected. In the last case a significant difference in risk might be expected in relatives of probands who possess compared with probands lacking these antigens. In the present study no significant difference in risk was found between these groups, which supports the hypothesis of linkage disequilibrium between these genes.

A genetic component has been established in psoriasis, but the mode of inheritance has been difficult to elucidate. Autosomal dominant inheritance with reduced penetrance (12, 24, 25), double recessive (12) and multifactorial inheritance (11, 26) have been suggested. As the present analysis has been based on a sample of psoriatics with no apparent genetic heterogeneity, estimations of the mode of inheritance seems possible. Simple monogenic inheritance with full penetrance can be excluded due to the fact that not all MZ pairs are concordant (2). The almost identical frequency of psoriasis in parents, siblings and children with no sex difference, is incompatible with autosomal recessive or X-linked inheritance, but not incompatible with autosomal dominant inheritance with reduced penetrance or multifactorial inheritance. A multifactorial origin is most likely according to analyses published by Watson et al. (11), and Ananthakrishnan et al. (26). Complex segregation analysis has been applied recently to Lomholts family material and the preliminary results (27) are in favour of a major locus for psoriasis with addition of a strong polygenic component. We have not tried to perform a segregation analysis of our data due to the relatively small sample and a somewhat lower diagnostic certainty than was present in the very complete family material collected by Lomholt (12).

A follow-up investigation of the youngest generation of unaffected children in Lomholt's pedigrees (12), who have passed the greater part of the manifestation period at the present time, as a basis for an up-dated segregation analysis, combined with HLA-typing of affected children, might form a unique basis for further information on inheritance and relation to the HLA haplotype.

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