Arch Dermatol Res (2002) 294 : 207–213
DOI 10.1007/s00403-002-0321-3

ORIGINAL PAPER

**Philip Stuart · Farah Malick · Rajan P. Nair
Tilo Henseler · Henry W. Lim · Stefan Jenisch
John Voorhees · Enno Christophers · James T. Elder**

Analysis of phenotypic variation in psoriasis as a function of age at onset and family history

Received: 30 October 2001 / Revised: 5 February 2002 / Accepted: 24 April 2002 / Published online: 13 June 2002

Abstract To evaluate the relationship between psoriasis disease severity, age at onset, and family history, we analyzed 537 US psoriatics, most of whom were from Michigan. Total body surface area involvement (%TBSA), presence or absence of joint complaints, and nail involvement were measured. Analysis of familial psoriatics revealed that %TBSA was 15.1% when onset was early, but only 8.7% when onset was late (P=0.00003). The opposite trend was seen when psoriasis was sporadic: %TBSA was 14.3% when onset was early (≤40 years of age) compared to 28.0% when onset was late (P=0.0034). However, the sporadic group was small and ascertainment of the sporadic group was biased for severe involvement. As determined by log-linear analysis, joint complaints and age at onset were not significantly associated after controlling for age at examination, nor were joint complaints and familial status. Psoriatic nail changes were conditionally independent of familial status, given age at onset; nail changes were more frequently encountered in early-onset patients. There was no significant difference in the frequency of carriage of the MHC psoriasis risk determinant in the familial vs sporadic groups. Early-onset psoriatics did carry this determinant significantly more frequently, as expected. These results demonstrate increased severity of skin and nail disease in early-onset psoriasis, when psoriasis is familial. The lack of clinical differences between "familial" and "sporadic" psoriasis may reflect a similar genetic basis for both conditions, at least when onset is early.

Keywords Psoriasis · Psoriatic arthritis · Nail diseases · Genetic variation

P. Stuart · R.P. Nair · J. Voorhees · J.T. Elder
Department of Dermatology, University of Michigan, Ann Arbor, Michigan, USA

F. Malick · H.W. Lim
Department of Dermatology, Henry Ford Health System, Detroit, Michigan, USA

T. Henseler · S. Jenisch · E. Christophers
Department of Dermatology, University of Kiel, Kiel, Germany

J.T. Elder
Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan, USA

J.T. Elder
Ann Arbor Veterans Affairs Hospital, Ann Arbor, Michigan, USA

J.T. Elder (✉)
3312 CCGC Building, 1500 E. Medical Center Drive, University of Michigan, Ann Arbor, MI 48109-0932, USA
e-mail: jelder@umich.edu,
Tel.: +1-734-7630355, Fax: +1-734-7634575

Introduction

Psoriasis is a common, inflammatory and hyperproliferative skin disease with a strong genetic basis (Elder et al. 2001). Early-onset psoriasis (age at onset ≤40 years) has been associated with a positive family history and with more severe disease (Henseler and Christophers 1985). The purpose of this study was to determine whether any differences in clinical presentation could be determined between patients with positive and negative family histories of psoriasis. To this end, we analyzed the psoriatic phenotype in a collection of subjects identified in the course of our search for the psoriasis genes (Nair et al. 1997; Nair et al. 2000). While this population is heavily skewed toward familial disease of juvenile onset, our findings confirm earlier associations between juvenile onset and disease severity, at least when psoriasis is familial. Our results also indicate that the differences between the clinical characteristics of "familial" and "sporadic" psoriasis are limited, at least when onset is early.

Subjects and methods

Subjects

All procedures involving human subjects were performed after obtaining informed consent under protocols approved by the Institutional Review Board of the University of Michigan. The diagnosis of psoriasis was established by physical examination by a dermatologist or by a dermatology resident, following published criteria

Table 1 Number of patients analyzed

	Early onset	Late onset	Total
Sporadic	214	13	227
Familial	236	74	310
Total	450	87	537

(Christophers and Sterry 1993). Cases in which the diagnosis was uncertain were excluded. All cases manifested chronic plaque and/or guttate psoriasis. Measures of disease severity included percent of total body surface area (%TBSA) (Fredriksson and Pettersson 1978), nail changes (pitting, oil spots, and/or onycholysis), and presence or absence of joint complaints. We did not require radiological evidence or visible deformity to categorize a patient as having joint complaints. Rheumatoid factor was not examined. The characteristics of the study population are presented in Table 1.

The sample consisted of 537 psoriatic individuals, most of whom were from Michigan. These individuals were randomly selected from our collection of psoriasis pedigrees and singletons with parents (Nair et al. 2000). Over 98% of the individuals came from families in which the index case was ascertained for early-onset psoriasis (≤40 years of age at onset); the remainder were ascertained for psoriasis at any age. Individuals were selected such that all individuals were genetically independent within any analysis category. In 227 individuals there was no known family history after a detailed interview; these individuals were considered to represent sporadic psoriasis. In 310 individuals, psoriasis was reported or demonstrated in at least one first-degree relative (not necessarily a living relative); these individuals constituted the familial psoriasis group.

Statistical analysis

Statistical analysis was performed by means of two-way analysis of variance (ANOVA), log-linear analysis (Fienberg 1980), *t*-tests, and chi-squares contingency table analysis. The details of ANOVA and log-linear analysis are presented below.

ANOVA

The sole quantitative variable measured was %TBSA involved at the time of ascertainment. Two-way ANOVA is the standard method to assess the variation of a numerical variable as a function of two categorical variables. ANOVA requires that the observations on the response variable are independent and normally distributed with equal variance for all combinations of the levels of the factors. However, the distribution of TBSA was highly skewed to the right for all four factor level combinations (skewness coefficient 2.19). By visual inspection of normal probability plots, and by maximum likelihood estimation, a natural logarithmic transformation was found to be the optimal choice among the Box-Cox family of power transformations for conversion to approximate normality in the US population (Box and Cox 1964). However, despite great improvement, the distribution of log-transformed %TBSA still deviated significantly from normality for one of the four treatment cell combinations [corrected $P=4.2\times10^{-3}$ by Lilliefors' test for normality (Lilliefors 1967)]. The residuals after application of standard ANOVA also deviate from normality in the US sample ($P=2.1\times10^{-4}$).

Although ANOVA is known to be robust to modest deviations from normality, a nonparametric alternative is to determine significance levels for the ANOVA using a randomization test rather than the *F*-distribution (Manly 1997). Randomization testing assumes only that the distribution of the response variable has the same shape for all treatment cells. Applying the Kolmogorov-Smirnov two-sample test to all six pairwise comparisons of four treatment cells in the US sample showed that the shapes of the log-transformed %TBSA distributions did not differ significantly from each other, if the distributions of each cell were first adjusted to have zero means. It was therefore appropriate to analyze the log-transformed %TBSA variable with two-factor ANOVA, when significance levels are determined by randomization. To accomplish this, 100,000 randomizations were performed. Each set of randomizations included the observed data. Therefore, the minimum randomization test *P*-value was 1×10^{-5}.

Log-linear analysis

Log-linear modeling is commonly used to analyze the relationships among factors of multinomial data. We followed the methods described by Fienberg (Fienberg 1980) for log-linear analysis. The goal of log-linear analysis is to find the simplest possible subset of the general log-linear model that fits the data well. For a three-dimensional table, the general model can be written as:

$$\log m_{ijk} = u + u_{1(i)} + u_{2(j)} + u_{3(k)} + u_{12(ij)} + u_{13(ik)} + u_{23(jk)} + u_{123(ijk)}$$

In this model, the logarithm of the expected value for the observation in the *i*th column, *j*th row, and *k*th layer of the three-way table ($\log m_{ijk}$) is a linear function of a grand mean u, the independent main effects of the three factors (u_1, u_2, u_3), all three possible two-way interactions among the three factors (u_{12}, u_{13}, u_{23}), and a three-way interaction term (u_{123}) which accounts for possible interactions between all two-factor interactions and the third factor.

The model as written is termed saturated because it contains all possible interaction effects at all possible levels; the saturated model always fits the data perfectly. Various unsaturated hierarchical models can be generated from the saturated model by setting one or more interaction effects (and their higher-order relatives) equal to zero. Each of these models can be fitted to a three-way table by iterative procedures, and the degree of fit assessed with either a Pearson chi-squared statistic or a likelihood ratio (LR) chi-squared statistic and their associated *P*-value. We chose that unsaturated model whose *P*-value was greater than 0.05, meaning that it fitted the data well. If more than one unsaturated model fitted the data well, we started at the most complicated good-fit model and compared it to the good-fit model of one step less complexity using a conditional LR statistic that was formed by subtracting the LR statistic for the more complex model from that of the simpler model. The conditional test statistic has an asymptotic chi-squared distribution under the null hypothesis, with degrees of freedom equal to the difference in the degrees of freedom of the two models. If the significance is less than the threshold, we chose the more complex model; otherwise we opted for the simpler model. If there were other good-fitting unsaturated models, the just-chosen simpler model was compared to the good-fit model of the next step lesser complexity. This model comparison procedure was repeated as often as necessary.

Log-linear analysis does not end with selection of the best unsaturated model (Lee 1978). Further steps may include examination of standardized cell residuals to better describe the nature of the association among the factors, collapsing of the three-way table to a two-way table when appropriate, and testing details of variable interactions by fitting models to partitions of the full table. The selection of the best log-linear model is crucial because it tells us the minimum structure necessary to adequately reproduce the data in the table, and all further hypothesis testing and description must conform to this structure in order to be valid.

Table 2 Disease severity in terms of %TBSA. Values are means±SD

	Early onset	Late onset	Total
Sporadic	14.3±17.9	28.0±21.7	15.1±18.4
Familial	15.1±19.5	8.7±15.1	13.5±18.7
Total	14.7±18.7	11.6±17.5	14.2±18.6

Table 3 ANOVA for ln(%TBSA)

Source of variation	Sum of squares	Degrees of freedom	Mean square	*F*	*F*-distribution *P*	Randomization *P*
Onset	0.472	1	0.472	0.37	0.545	0.547
Familial	25.99	1	25.99	20.22	8.49×10^{-6}	1.00×10^{-5}
Interaction	26.96	1	26.96	20.98	5.80×10^{-6}	1.00×10^{-5}
Error	685.1	533	1.285			

Table 4 *P*-values for stratified effects of two categorical variables on ln(%TBSA), as determined by two-sample *t*-tests

	Early vs late onset		Non-familial vs familial
Sporadic	3.4×10^{-3}	Early onset	8.9×10^{-1}
Familial	3.0×10^{-5}	Late onset	1.0×10^{-5}

Results

Analysis of TBSA

Our first analysis asked whether and how %TBSA depends upon two categories: age at onset (early vs late) and type of psoriasis (familial vs sporadic). The means and standard deviations of the %TBSA for each category are presented in Table 2. The results of the two-way ANOVA on ln(%TBSA) are shown in Table 3. Significance levels were determined both by the ordinary parametric method (*F*-distribution *P*) and by 100,000 randomizations (randomization *P*). The significance levels determined by these two tests were very similar, indicating that the standard test is quite robust to the deviation from normality of the distribution of ln(%TBSA). The interaction of the two main effects (onset and familial) was highly significant, which means that the effect of one of the factors upon %TBSA depended upon the level of the second factor. Because of this interaction, it was necessary to compare the effects of each factor only within a single level of the other factor. To do this, a two-sample *t*-test with pooled variances was employed, with significance levels again being determined by 100,000 randomizations. Two-tailed *P*-values for all four two-sample tests are shown in Table 4. The effect of age at onset on %TBSA was highly significant for both non-familial and familial psoriatics, but the direction of the effect depended upon the type of psoriasis: for familial psoriatics %TBSA was greater when onset was early (15.1% vs 8.7%), whereas for sporadic psoriatics %TBSA was less when onset was early (14.3% vs 28.0%). The effect of familial status on %TBSA was significant only for late-onset patients, with sporadic patients having a much greater mean %TBSA than familial patients (28.0 vs 8.7%).

Analysis of joint complaints

We next assessed the influence of age at onset (early or late) and type of psoriasis (familial or sporadic) on the incidence of joint complaints. Because it is known that joint complaints of all types are more common in older people, we used the age at examination as a controlling factor for joint complaints. Patients were cross-classified for four factors (age at onset, age at examination, joint complaints, and familial psoriasis), and analyzed by log-linear modeling. Ideally, we would have liked to analyze a four-way table, but because many of the cells were empty when our patients were simultaneously classified by all four factors, we resorted to analysis of three-way tables instead. Because it is crucial to control for age at examination, this factor and the response of joint complaints must both be included, so the third factor became age at onset for one three-way table and familial status for the other. The descriptive statistics are available on request.

Log-linear modeling of the classification of joint complaints×age at onset×age at examination revealed that the simplest model that fitted the data well was one in which joint complaints and age at onset were not related to each other, as long as age at examination was controlled for (details available on request). Because this model indicated that joint complaints was related to both age at examination and age at onset, it was necessary to include age at examination as a controlling factor. As illustrated in Table 5, there was no significant association of joint com-

Table 5 Frequency of joint complaints by age at onset, stratified by age at examination

Age at examination (years)	Joint complaints (%)		Relative risk	Pearson χ^2	*P*-value
	Early onset)	Late onset			
0–20	0.0	–	–	–	–
21–30	16.9	–	–	–	–
31–40	33.1	–	–	–	–
41–50	24.0	28.6	1.25	0.12	0.72
51–60	47.4	47.1	0.99	0.00069	0.98
>60	42.9	44.2	1.06	0.012	0.91
Total	25.1	42.9	2.24	11.92	0.00056

Table 6 Frequency of joint complaints by familial status, stratified by age at examination

Age at examination (years)	Joint complaints (%)		Relative risk	Pearson χ^2	*P*-value
	Sporadic	Familial			
0–20	0.0	0.0	–	–	–
21–30	14.6	19.4	1.41	0.32	0.57
31–40	26.6	40.9	1.91	3.33	0.068
41–50	20.5	26.8	1.42	0.43	0.51
51–60	47.1	47.3	1.01	0.00024	0.99
>60	28.6	45.3	2.07	0.72	0.40
Total	19.7	34.0	2.09	13.32	0.00026

plaints and age at onset within an age at examination cohort. However, as the incidence of joint complaints tends to increase with age, when all age at examination cohorts were lumped together, a strong association appeared to exist, with late-onset patients apparently having twice the risk of joint complaints as early-onset patients. The association was spurious because the greater incidence of joint complaints among late-onset psoriatics was due to their greater mean age.

Turning to the classification of joint complaints×familial status×age at examination, log-linear modeling indicated that the simplest model that fitted the data well was one in which joint complaints and familial psoriasis were conditionally independent given age at examination, but that age at examination was not independent of joint complaints or of a family history of psoriasis (details available upon request). The association of age at examination with each of the other factors was positive, and collapsing the three-way table into two-way tables allowed the most powerful possible significance tests for these interactions ($P=6.4\times10^{-11}$ for age at onset and joint complaints and $P=1.9\times10^{-13}$ for age at onset and familial status). The importance of controlling for the effects of age at examination is illustrated by Table 6. It is clear that the twofold relative risk for joint complaints of familial versus sporadic psoriasis that resulted is spuriously high when the table is collapsed over age at examination. For none of the age cohorts did the relationship of joint complaints and familial status become significant; hence the finding of conditional independence of these two factors.

Analysis of nail involvement

We next assessed the influence of age at onset and type of psoriasis (familial or sporadic) on the incidence of nail involvement. Although age at examination was not suspected a priori as a factor affecting nail involvement, our finding that age at examination was positively correlated with both age at onset and familial history indicated that we should consider age as a potential controlling factor for nail disease as well. As before, our sample size dictated analysis of three-way partitions of the full four-way table. Age at examination may or may not be an important factor, so we analyzed all possible three-way tables that had nail involvement as a response. We also performed separate analyses for fingernail involvement and toenail involvement, because fungal infections often affect toenail appearance in a way that can be difficult to distinguish from psoriasis. Details of this analysis are available upon request.

Log-linear modeling of the classification of nail involvement×familial status×age at onset revealed that the simplest model that fitted the data well was one in which both fingernail and toenail involvement were independent of familial status when controlling for age at onset. Both nail variables were associated with age at onset, and age at onset was associated with familial status. Collapsing the full table over familial status showed that fingernail involvement was negatively associated with age at onset (relative risk 0.38, $P=7.7\times10^{-5}$; Table 7), as was toenail involvement (relative risk 0.45, $P=6.5\times10^{-3}$; Table 8). Reducing the table by lumping the nail categories yielded a strong positive association of age at onset with familial status (relative risk 5.4, $P=5.8\times10^{-9}$). This association was an artifact of our sampling procedure, as over 90% of the US sporadic cases were ascertained for age at onset <40 years. This association was actually the opposite of what is seen for psoriasis in general (Henseler and Christophers 1985).

Log-linear modeling of the classification fingernail involvement×age at onset×age at examination revealed that the simplest model that fitted the data well was one in which fingernail involvement was negatively related to age at onset but positively related to age at examination, while age at onset and age at examination were positively correlated as seen before in the analysis of joint complaints (details available on request). The magnitude of the negative association of fingernail involvement and age at onset was assessed by examining this association within separate cohorts for age at examination (Table 7). Note that the relative risk of 0.38 for the combined data only equals that of the oldest cohort (age >60 years) and is not nearly as extreme as that of the other two cohorts for which we were able to make the comparison (0.062 for age 41–50 years and 0.14 for age 51–60 years).

Log-linear modeling of the classification toenail involvement×age at onset×age at examination revealed that only the full saturated model fitted the data well; that is, all pairs of factors were significantly associated and the degree of this association depended upon the level of the third factor (details available upon request). Thus, it was not valid to test the significance of two-factor interactions

Table 7 Fingernail involvement as a function of age at onset, stratified by age at examination

Age at examination (years)	Fingernail involvement (%)		Relative risk	Pearson χ^2	*P*-value
	Early onset	Late onset			
0–20	32.4	–	–	–	–
21–30	45.5	–	–	–	–
31–40	51.0	–	–	–	–
41–50	55.2	7.1	0.062	11.29	7.8×10^{-4}
51–60	68.4	23.5	0.14	14.51	1.4×10^{-4}
>60	60.7	37.2	0.38	3.77	0.052
Total	50.1	27.5	0.38	15.63	7.7×10^{-5}

Table 8 Toenail involvement as a function of age at onset, stratified by age at examination

Age at examination (years)	Toenail involvement (%)		Relative risk	Pearson χ^2	*P*-value
	Early onset	Late onset			
0–20	15.5	–	–	–	–
21–30	27.3	–	–	–	–
31–40	29.7	–	–	–	–
41–50	37.5	0.0	0.00	7.80	5.2×10^{-3}
51–60	44.7	11.8	0.16	9.44	2.1×10^{-3}
>60	39.3	25.6	0.53	1.49	0.22
Total	30.6	16.5	0.45	7.40	6.5×10^{-3}

apart from the third factor. As with fingernail involvement, the strength of negative association between toenail involvement and age at onset decreased as age at examination increased (Table 8). This trend was stronger for toenail involvement, as relative risk increased from 0.00 to 0.53 for toenail involvement, as compared to an increase in relative risk from 0.06 to 0.38 for fingernail involvement. The variation in strength of association among age cohorts reached significance for toenail involvement, but not for fingernail involvement (P=0.043 for toenail, P=0.16 for fingernail).

Log-linear modeling of the classification nail involvement×familial status×age at examination revealed that the simplest model that fitted the data well was one in which familial status and age at examination were associated, but that the factors comprising this association were jointly independent of nail involvement (fingernail or toenail). Given this structure, we were able to collapse the three-way table over each of the factors in turn to describe the relationship between all pairs of factors. Doing so yielded no significant relationship of fingernail or toenail involvement with either familial status or age at examination. As noted earlier in the analysis of joint complaints, there was a strong positive association between familial status and age at examination ($P=1.9\times10^{-13}$). This association reflected ascertainment bias and is not true of the general population of psoriatics (Henseler and Christophers 1985).

Analysis of MHC risk haplotype

The previous analyses suggested that age at onset had more effect on psoriasis phenotype than did familial status. Therefore, we wished to test the hypothesis that early and late onset psoriatics differ genetically for carriage of a psoriasis disease allele, whereas sporadic and familial psoriatics do not. This analysis was possible because most of the sample had been characterized genetically for the presence or absence of Risk Haplotype 1 (RH1), a 60-kb stretch of DNA just telomeric to HLA-C. By analysis of recombinant ancestral haplotypes, we have shown that RH1 is likely to carry the disease allele at PSORS1, and that over 60% of psoriatics in the US sample are identical by descent for this allele (Nair et al. 2000).

A total of 426 American patients were cross-classified for familial status, age at onset, and RH1 haplotype, and analyzed by a chi-squared test of independence of either age at onset or familial status with possession of the RH1 haplotype (Table 9). The RH1 factor has two categories if

Table 9 Cross-classification of RH1 carriage with familial status and age at onset

RH1 genotype	Familial status			Age at onset		
	Sporadic	Familial	Total	Early	Late	Total
+/+	9	22	31	28	3	31
+/–	81	130	211	185	26	211
–/–	79	105	184	145	39	184
Total	169	257	426	358	68	426

we do not distinguish between carriage of one or two copies of the haplotype, and three categories otherwise. For familial status, Pearson's chi-squared statistic was 2.43 (P=0.30) when all three RH1 categories were retained, and 1.44 (P=0.23) when the $RH1^{+/-}$ and $RH1^{+/+}$ categories were lumped. Hence, even though familial psoriatics had one or two copies of RH1 more frequently than did sporadic individuals (59.1% vs 53.2%), this difference was not large enough to reach statistical significance. In contrast, the greater incidence of RH1 in early-onset psoriatics (59.5% vs 42.7%) was significant, whether all three RH1 categories were retained (P=0.034) or the $RH1^{+/-}$ and $RH1^{+/+}$ categories were lumped (P=0.010).

Discussion

These studies were undertaken in an effort to determine whether the clinical manifestations of familial psoriasis differ detectably from those of so-called "sporadic cases". For this purpose, we analyzed a sample of 537 US patients drawn mainly from the southeast Michigan area. Because most of these patients had been collected for a genetic study of juvenile-onset familial psoriasis, nearly all (98%) belonged to families ascertained on the basis of age at onset ≤40 years in the index case in that family. These patterns of ascertainment were not optimal for addressing the question we wished to address; therefore, we gave considerable thought to the statistical methods used for our analysis. It is important to keep this ascertainment bias in mind while interpreting our results.

ANOVA indicated that age at onset and familial status interact with each other to affect the magnitude of %TBSA (Table 3). For familial psoriasis, %TBSA was 15.1% when onset was early, but only 8.7% when onset was late (P=0.00003, Table 4). The opposite trend was seen when psoriasis was sporadic: %TBSA was 14.3% when onset was early compared to 28.0% when onset was late (P=0.0034, Table 4). If the interaction between age at onset and familial status had been ignored, we would have missed the opposing trends in the effect of age at onset on %TBSA for familial vs non-familial psoriasis.

The number of patients with non-familial, late-onset disease was quite small in the US sample (13 patients). Three of these patients were recruited from the dermatology clinic, two were recruited from the phototherapy unit, and seven were recruited from responses to mass mailings, and one patient responded to a newspaper advertisement. Thus, 4 of the 13 individuals (31%) in this subgroup were actively seeking intensive therapy at the time of ascertainment. This compares to 11 of 215 (5.1%) in the early-onset, non-familial group, 16 of 240 (6.7%) in the early-onset, familial group, and 6 of 77 (7.8%) in the late-onset, familial group. Thus, there were at least two potential sources of error in the non-familial, late-onset subgroup: small sample size and ascertainment bias for more severe disease. For early-onset patients, who comprised 84% of the patients in this analysis, no significant difference in %TBSA was observed for familial versus sporadic cases (14.3±17.9% vs 15.1±19.5%, P=0.89; Tables 2 and 4). Therefore, we believe that there is unlikely to be a biologically meaningful difference in TBSA between sporadic and familial psoriasis. However, further studies will be necessary to fully explore the interaction of age at onset and familial status with respect to disease severity.

We next assessed the effects of familial status on two well-recognized psoriatic phenotypes: joint complaints and nail involvement (Christophers and Sterry 1993). We found that joint complaints and age at onset were not significantly associated if age at examination was controlled for (Table 5). Joint complaints and familial status were also not significantly associated when controlling for age, although a modest increase in joint complaints among familial psoriatics might have reached statistical significance in a larger sample (Table 6).

Both fingernail and toenail abnormalities were conditionally independent of familial status, given age at onset. Fingernail and toenail involvement were also jointly independent of familial status and age at examination, so it was unnecessary to control for age at examination to demonstrate the lack of association between nail involvement and familial status. On the other hand, fingernail and toenail abnormalities were both observed significantly less often in the late-onset group (Tables 7 and 8). The magnitude of this association decreased with increasing age at examination, although this trend reached statistical significance only for toenail involvement. By inspection of the juvenile-onset group in Tables 7 and 8, it is evident that there was an increase in fingernail and toenail findings with duration of disease. This observation is in agreement with previous reports (de Jong et al. 1996; Tham et al. 1988).

RH1 is a robust marker for the presence of an ancestral disease allele at PSORS1, the MHC locus that appears to play a major role in the genetics of psoriasis (Elder et al. 2001; Nair et al. 2000). A similar fraction of sporadic and familial psoriatics in the US sample carried RH1 (59.1% for familial vs 53.2% for sporadic, P=0.23). In contrast, a significant difference in RH1 carriage was observed between early onset and late onset groups (59.5% vs 42.7%, P=0.01). This finding suggests that so-called "familial" and "sporadic" psoriasis may have a similar genetic basis.

How can "sporadic" psoriasis have a genetic basis? It is instructive here to consider the fact that the penetrance of the PSORS1 disease allele is only approximately 10%; i.e., 90% of PSORS1 disease allele carriers are unaffected (Elder et al. 2001). While environmental factors may play an important role in limiting the penetrance of PSORS1, the existence of additional unlinked loci, also required for development of disease, is an alternative explanation with experimental support. Evidence has been presented for at least nine different psoriasis susceptibility loci in genetic linkage studies (Elder et al. 2001). Four of these loci have been reported as carrying at least suggestive evidence for linkage by at least two groups (Elder et al. 2001), and two of them are generally regarded as confirmed (Altmuller et al. 2001). If one assumes that disease alleles at each of four distinct loci are required to develop psoriasis, that

each disease allele acts in a dominant fashion, and that each disease allele is completely penetrant, then one can readily envision a nuclear pedigree in which one copy of each disease allele is distributed between the parents such that no single parent carries all four (father could have one and mother three, father two and mother two, or father three and mother one). Neither parent would be affected, and the chance of any given child developing psoriasis would be $(1/2)^4=1/16$. Such a family would need to be quite large in order to observe more than one case per nuclear family. In most such families, no second case would be identified, the disease would be considered to be sporadic.

Evidence for linkage of psoriasis to PSORS1 appears to be far stronger than that for any other locus (Elder et al. 2001), and therefore likely to have a pronounced effect on the phenotype. The very similar carriage rates of the PSORS1 disease allele between familial and sporadic groups argues that this distinction between "familial" and "sporadic" psoriasis may be more apparent than real. Because over 90% of the individuals in the US sporadic group were ascertained for early-onset psoriasis, it is prudent to limit this conclusion to early-onset psoriatics for the time being. We must also acknowledge the possibility that a subset of sporadic psoriatics do in fact have a non-genetic basis. Nevertheless, if our conclusion is correct in the main, then the presence of the same genetic factors in both groups is sufficient to explain the similarity of disease phenotype in patients who we have categorized as "familial" and "sporadic".

Acknowledgements We thank Drs. Nicholas Chia, Christopher Bichakjian, Margaret Terhune, Michael Woodbury, and Jane Kim for their assistance with clinical evaluation. Our special thanks are extended to the patients and family members who participated in the familial psoriasis study. This research was supported by USPHS award R01 AR4274-01 (J.T.E., R.P.N., J.J.V.), by award DFG-WE 905/1-1 from the German Research Foundation (T.H., S.J., E.C.), by the Ann Arbor Veterans Affairs Hospital (J.T.E.), and by the Babcock Memorial Trust.

References

Altmuller J, Palmer LJ, Fischer G, Scherb H, Wjst M (2001) Genomewide scans of complex human diseases: true linkage is hard to find. Am J Hum Genet 69:936–950

Box GEP, Cox DR (1964) An analysis of transformations (with discussion). J R Stat Soc B 26:211–252

Christophers E, Sterry W (1993) Psoriasis. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF (eds) Dermatology in general medicine. :McGraw-Hill, New York, pp 489–514

de Jong EM, Seegers BA, Gulinck MK, Boezeman JB, van de Kerkhof PC (1996) Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. Dermatology 193:300–303

Elder JT, Nair RP, Henseler T, Jenisch S, Stuart P, Chia N, Christophers E, Voorhees JJ (2001) The genetics of psoriasis 2001: the odyssey continues. Arch Dermatol 137:1447–1434

Fienberg SE (1980) The analysis of cross-classified categorical data. MIT Press, Cambridge (Mass.) London

Fredriksson T, Pettersson U (1978) Severe psoriasis – oral therapy with a new retinoid. Dermatologica 157:238–244

Henseler T, Christophers E (1985) Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 13:450–456

Lee SK (1978) An example for teaching some basic concepts in multidimensional contingency table analysis. Am Statistician 32:69–71

Lilliefors HW (1967) On the Kolmogorov-Smirnov test for normality with mean and variance unknown. J Am Stat Assoc 64: 399–402

Manly BFJ (1997) Randomization methods: randomization, bootstrap, and Monte Carlo methods in biology. Chapman & Hall, London

Nair RP, Henseler T, Jenisch S, Stuart P, Bichakjian CK, Lenk W, Westphal E, Guo SW, Christophers E, Voorhees JJ, Elder JT (1997) Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. Hum Mol Genet 6:1349–1356

Nair RP, Stuart P, Henseler T, Jenisch S, Chia NV, Westphal E, Schork NJ, Kim J, Lim HW, Christophers E, Voorhees JJ, Elder JT (2000) Localization of psoriasis-susceptibility locus PSORS1 to a 60-kb interval telomeric to HLA-C. Am J Hum Genet 66: 1833–1844

Tham SN, Lim JJ, Tay SH, Chiew YF, Chua TN, Tan E, Tan T (1988) Clinical observations on nail changes in psoriasis. Ann Acad Med Singapore 17:482–485