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INVESTIGATIVE REPORT

Genetic Factors Explain Variation in the Age at Onset of Psoriasis: A Population-based Twin Study

Ann Sophie LØNNBERG[1], Lone SKOV[1], David Lorenzo DUFFY[2], Axel SKYTTHE[3], Kirsten Ohm KYVIK[4], Ole Birger PEDERSEN[5] and Simon Francis THOMSEN[1]

[1]Department of Dermato-Allergology, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, [2]Queensland Institute of Medical Research, Brisbane, Australia, [3]The Danish Twin Registry, University of Southern Denmark, [4]Institute of Regional Health Services Research, University of Southern Denmark, Odense, Denmark and Odense Patient data Explorative Network (OPEN), Odense University Hospital, Odense, and [5]Department of Clinical Immunology, Naestved Hospital, Naestved, Denmark

The aim of this study was to determine the age at onset of psoriasis in a population-based twin sample. Questionnaire-data in 10,725 twin pairs, 20–71 years of age, from the Danish Twin Registry, was collected, and analysed using survival regression analysis. Median age at onset was 25 and 28 years among women and men, respectively. The correlation between the ages was 0.84 (bootstrap standard error=0.044) in monozygotic twin pairs and 0.60 (0.051) in dizygotic twin pairs, permutation $p=0.001$. Age at onset of psoriasis in the index twin did not predict risk of psoriasis in the co-twin, hazard ratio (per year of later onset =1.01 (0.99–1.03), $p=0.434$. In conclusion, these data support that the age at onset of psoriasis is, in part, an inherited property. Our results do not support that early-onset psoriasis is more genetically determined. ***Key words: Age at onset; psoriasis; twins; twin study; genetic.***

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Lone Skov, Department of Dermato-Allergology, Gentofte Hospital, Niels Andersens Vej 65, DK-2900 Hellerup, Denmark. E-mail: Lone.Skov.02@regionh.dk

Psoriasis is a chronic inflammatory disease characterized by uncontrolled proliferation of keratinocytes, activated dendritic cells, release of proinflammatory cytokines and recruitment of T cells into the skin (1, 2). Psoriasis affects approximately 2–3% of all Caucasians (3, 4). The first skin manifestations can occur at any age; however, 2 peaks in age at onset have been described, the first at approximately 16 years of age (in females) or 22 years of age (in males), and the second at approximately 60 years of age (in females) or 57 years of age (in males). Approximately 75% of patients develop the disease before the age of 40 years (5, 6).

The 2 peaks in age at onset have given rise to the hypothesis that 2 forms of the disease exist: psoriasis of early-onset, which is likely to be familial, and psoriasis of late-onset, which is more likely to be sporadic and non-familial. Family studies have indicated that age at onset is an inherited property (5, 7–9). This is also supported by genetic studies, which have shown that early-onset psoriasis is associated with variation in the human lymphocyte antigen (HLA), whereas late-onset psoriasis has only a weak association with HLA (5, 10, 11).

A few twin studies have investigated age at onset of psoriasis (12–17). However, this was not the primary objective of these studies and most of them examined an insufficient number of twins. Consequently, the aim of this study was to examine age at onset of psoriasis in a large twin sample. Specifically, we used data from the Danish Twin Registry on physician-diagnosed psoriasis in 34,781 twin subjects in order to study familial correlation in age at onset of psoriasis.

METHODS

Population

The studied sample comprised twins born between 1931 and 1982 who were registered in the nationwide Danish Twin Registry. We have previously reported recurrence risks and heritability of psoriasis for this population (18). The population constituted 2 separate cohorts of twins, ascertained differently by the registry (19–21). The first cohort included twins born between 1931 and 1952. This cohort was identified and enrolled in the Danish twin registry in 1996 and corresponded to 69% of all twin pairs born in Denmark during these years. The second cohort included twins born between 1953 and 1982. This cohort was identified and enrolled in the Danish Twin Registry in 1991 and corresponded to 74% of all twin pairs born in Denmark between 1953 and 1967 and 97% of all twin pairs born in Denmark between 1968 and 1982.

In 2002, these cohorts participated in a multidisciplinary questionnaire study concerning health and lifestyle including questions on psoriasis. A history of psoriasis was defined as an affirmative response to the question: "Has a doctor ever told you that you have, or have had psoriasis?" In addition to this question study participants were asked to report the age at which their disease occurred first; this information defined the age at onset of psoriasis. Twin zygosity was determined using 4 questions of similarity and mistaken identity, which assign zygosity correctly in more than 95% of cases (22). The 2 cohorts were 20–49 and 50–71 years of age, respectively, when answering the questionnaire. The response rate to the questionnaire was 75%.

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Statistical analysis

A Cox proportional hazards regression model was fitted with the time to onset of psoriasis in the co-twin of an affected twin (the index twin) as the underlying time, and with zygosity, and age at onset of psoriasis in the index twin as covariates. In this analysis an increased hazard ratio (HR) in monozygotic (MZ) twins relative to dizygotic (DZ) twins would signal a genetic susceptibility to psoriasis. The regression analysis was performed in SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). The cumulative hazard of psoriasis in twin pairs was calculated with the statistical software R assigning one twin randomly as the proband. We also examined the correlation between the ages at onset of psoriasis within twin pairs using bivariate survival analysis under several different models. Firstly, we calculated rank correlations ("normalized" Kendall's tau) in age at onset using twin pairs where the ordering was unambiguous, as per Oakes (23). We used bootstrapping to estimate standard errors, and permuted zygosity labels to test for equality of MZ and DZ twin correlations. We compared these results with those from a gamma-frailty bivariate survival analysis (Clayton-Oakes-Glidden model) using both the R *mets* and *parfm* packages (24, 25).

RESULTS

Descriptive analysis of the cohort

In total, 34,781 subjects participated in the questionnaire study. Of these, 97% (33,588) had complete data on psoriasis. A total of 12,927 subjects were from the cohort born in 1931–1952, and a total of 20,661 subjects were from the cohort born in 1953–1982. The zygosity was identified in 32,651 subjects. Of these 21,450 twin individuals had complete data on psoriasis and belonged to an intact twin pair (10,725 pairs in total); 3,246 monozygotic (MZ) twin pairs and 7,479 dizygotic (DZ) twin pairs (4,010 same sex and 3,469 opposite sex). Psoriasis was present in 1,401 twins. Of these, 896 subjects (64%) also reported their age at onset; 68% of the women and 58% of the men. The non-responders were, on average, older than responders (49.1 vs. 45.7 years). The mean age of the population was 44.5 years and the prevalence of psoriasis was 4.2%.

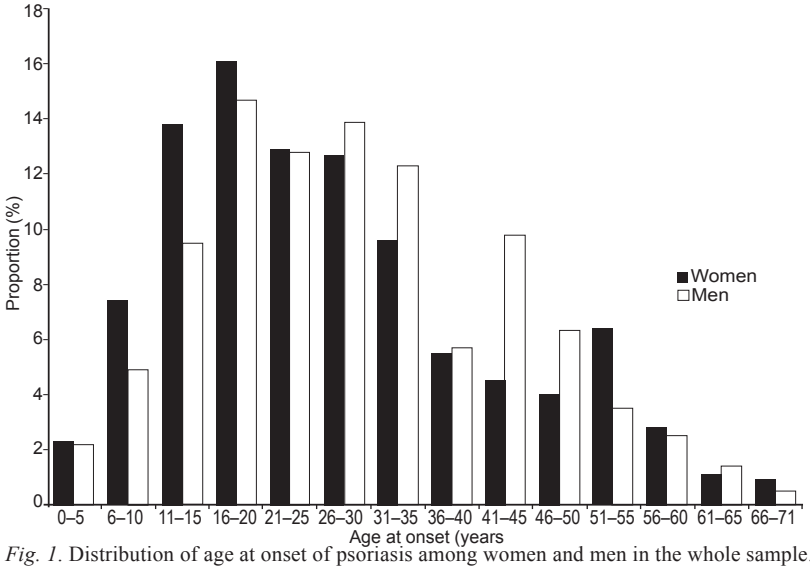

Fig. 1. Distribution of age at onset of psoriasis among women and men in the whole sample.

Age at onset of psoriasis in the whole sample

Among subjects with psoriasis, the median age at onset was 25 years among women and 28 years among men. The distribution of age at onset of psoriasis defined 2 age-related groups: a major group with peak age at onset in the mid-20s (lowest among women), and a smaller late-onset group with a peak age at onset around 50 years (lowest among men) (Fig. 1). A total of 80% of women and 76% of men had early onset of psoriasis (≤40 years of age), whereas before or at the age of 30 years 65% of women and 58% of men had developed psoriasis.

Age at onset of psoriasis within twin pairs

Of 820 twin pairs with complete information on age at onset, a total of 99 pairs (45 MZ, 30 DZ same sex, and 24 DZ opposite sex pairs) were concordant for psoriasis, whereas 721 (179 MZ, 270 DZ same sex, and 272 DZ opposite sex pairs) were discordant.

Fig. 2 shows the risk of psoriasis in the co-twin of an affected twin for MZ and DZ same sex twins separately, as a function of age at onset in the index twin. After adjustment for age at onset of psoriasis in the index twin, the risk of psoriasis was increased in MZ co-twins relative to DZ co-twins, HR = 2.16 (1.37–3.40), $p < 0.001$. The risk of psoriasis in the co-twin was not significantly related to age at onset of psoriasis in the index twin, HR (per year of later onset) = 1.01 (0.99–1.03), $p = 0.434$, indicating that familial aggregation of psoriasis is uniform across ages.

The estimated rank correlations (Kendall tau) in the ages at onset of psoriasis within twin pairs was 0.84 (bootstrap SE = 0.044) in MZ twin pairs and 0.60 (0.051) in DZ twin pairs, permutation p for difference between MZ and DZ twins $p = 0.001$. MZ female and male pairs did not differ significantly in within-pair correlation from one another, as was also the case for DZ pairs. On dividing the pairs into current age below or above 40 years, the DZ correlation in age at onset was significantly higher for older than for younger twins (tau 0.68 vs. 0.29, permutation $p = 0.01$), but in the smaller MZ sample did not reach significance. We also dichotomized age at onset into prior to 20 years old vs. later, and defined the index twin as the earliest affected. If the index twin had an onset before 20 years, a late onset in the co-twin was seen in only 9

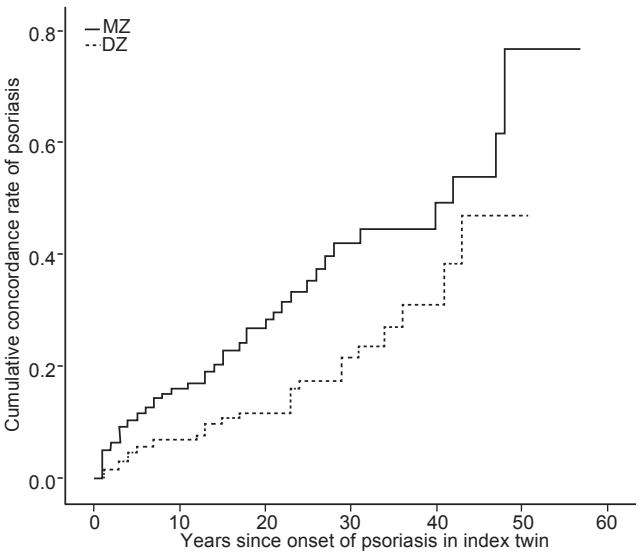

Fig. 2. Risk of developing psoriasis in the co-twin of an affected twin, as a function of age at onset in the index twin. Monozygotic (MZ) and dizygotic (DZ) same sex twins are illustrated separately.

of 589 pairs; if the index twin onset was after 20 years, 161 of 348 co-twins had been diagnosed with psoriasis.

DISCUSSION

The main conclusions of this study are: (*i*) overall, women have an earlier age at onset of psoriasis than men; however, there is a bimodal age-distribution of onset of psoriasis, with a primary peak at around 20 years of age (lowest among women), and a second peak at around 50 years of age (lowest among men); (*ii*) the age at onset of psoriasis is significantly more correlated among MZ twin pairs than among DZ twin pairs, consistent with genetic factors explaining part of the variation in the age at onset of the disease; and (*iii*) there is no consistent evidence to support the hypothesis that early-onset psoriasis is more familial (genetic) than late-onset psoriasis exemplified by the observation that earlier onset of psoriasis in the index twin did not predict a higher risk of psoriasis in the co-twin.

A median age at onset of psoriasis of 25 years among women and 28 years among men is comparable with previous studies (12, 13, 15, 17, 26–28). Some studies have examined a young population, which gives a low age at onset of psoriasis (14, 16). The age of the subjects at the time of examination differs between previous studies. In our study the subjects were 20–71 years old. Studies of subjects with an older age at examination can be expected to find a more accurate mean age at onset (12, 13); however, these studies are more susceptible to recall bias. The younger age at onset in females compared with males is compatible with findings from earlier studies and has been attributed partly to puberty (5, 14, 16, 26).

Our data suggest 2 age-related peaks in psoriasis-onset. Similar peaks have been found in previous studies and this has given rise to the hypothesis that 2 forms of psoriasis exist: early-onset psoriasis, which is more severe and inherited (type 1); whereas late-onset psoriasis is less severe and sporadic (type 2). In contrast to our study, which is population-based, most prior studies are based on physician-diagnosed samples. Most previous studies are therefore selected and not random, which increases the risk of ascertainment and referral bias and an overestimate of the heritability of early-onset psoriasis, since such studies are more prone to selecting severe cases of the disease. A study by Melski & Stern from the USA (29) found that early-onset psoriasis is more heritable and that age at onset aggregates within families; however, they found no association of age at onset with severity, but their population was composed of patients with severe psoriasis. Specific genes have previously been found to be associated with early-onset psoriasis (5, 10, 11, 30). Genome-wide association studies of psoriasis have focused primarily on early-onset psoriasis and have identified a total of 36 loci associated with psoriasis (31). Hébert et al. (32) investigated the genetic susceptibility to late-onset psoriasis and found a genetic overlap with early-onset psoriasis, but also found loci that were exclusively associated with late-onset psoriasis. This explains and supports the finding that age at onset is an inherited property. Swanbeck et al. (33) from Sweden advocate 3 distinct groups of patients with respect to age at onset, and that age at onset is an inherited character. Ejaz et al. (28) studied a population from Pakistan and found no significant differences in severity and family history between 2 age-related groups when assigning early-onset psoriasis to occur before the age of 30 years.

Based on the observed distribution of age at onset of psoriasis we assigned early-onset to occur before or at the age of 40 years to make sure the first peak was in this group. This definition of the groups is consistent with prior studies; however, some studies have set early-onset psoriasis to occur before 30 years, which makes it more difficult to compare results. In our dataset 80% of women and 76% of men had early-onset psoriasis, which is congruent with earlier studies of large populations (Table SI[1]).

The rank correlation between ages at onset of psoriasis was 0.84 and 0.60 in MZ twins and DZ twins, respectively, consistent with the hypothesis that genetic factors explain part of the variation in the age at onset. Duffy et al. (17) found almost a perfect linear regression when plotting the ages at onset of psoriasis in concordant MZ twins. Swanbeck et al. (9) investigated families with 1 proband and 2 affected siblings, and estimated the correlation between the age at onset in the proband and the first sibling to be 0.40, and between the 2 affected siblings to be 0.42. Differences in MZ twins might be due to unmeasured epigenetic factors rather than the

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environment alone. However, epigenetics might also be an inherited factor and could thereby influence the genetic component (34).

We diagnosed psoriasis and its age at onset based on answers to a questionnaire with a resulting risk of false-positive and false-negative answers, and also of recall-bias. However, diagnostic validation of psoriasis in our sample confirmed the diagnosis in 89–100% of the twins (15). The Danish Twin Registry is among the largest and most comprehensive twin registries in the world. The results of this study are therefore of unique significance.

We conclude that the age at onset of psoriasis is partly an inherited property exemplified by the observation that age at onset of the disease is more correlated in MZ than in DZ twins. We did not confirm previous studies' reports that early-onset psoriasis is more genetically determined than late-onset psoriasis. Finally, women have an earlier age at onset of psoriasis than men. The age distribution curve is bimodal, with a primary peak at around 20 years of age and a second peak at around 50 years of age.

The authors declare no conflicts of interest.

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