On the heritability of psoriatic arthritis. Disease concordance among monozygotic and dizygotic twins

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ABSTRACT

Objective: A nationwide unselected twin population to estimate the relative importance of genetic and environmental effectors in the aetiopathogenesis of psoriatic arthritis (PsA).

Methods: The study comprised three Danish nationwide twin cohorts. In 1994 and 2002 a total of 37 388 and 46 418 Danish twin individuals respectively were asked by questionnaire if they had PsA. Twins reporting PsA were invited to participate in a clinical examination. Patients were classified according to the Moll and Wright and the CASPAR (CIASsification criteria for Psoriatic ARthritis) criteria. Heritability was estimated by proband-wise concordance rates and variance component analysis.

Results: 228 twin individuals reported PsA. Following diagnostic validation in 164 (70%), 50 probands were diagnosed with PsA according to the Moll and Wright criteria. Five of their co-twins were either dead, had emigrated, or did not participate in the twin study and nine did not respond, resulting in 36 complete pairs. A total of one of 10 monozygotic pairs and one of 26 dizygotic pairs were concordant for PsA, yielding a 6.2% difference in proportions (95% CI: −11%, 37%). Five of 10 monozygotic pairs and four of 26 dizygotic pairs were concordant for psoriatic skin disease implying a 35% difference (95% CI: 2%, 60%, $p<0.05$).

Conclusions: This first twin study on PsA confirms that genes are important in the causation of psoriatic skin disease. Despite the limited statistical power, the almost identical concordance rates for PsA in monozygotic and dizygotic twins stresses the importance of the continued search for non-genetic effectors in PsA.

Previous twin and family studies suggest that genes play a major part in the development of psoriasis.[1–3] The relative importance of genes and environmental factors for the development of inflammatory joint disease in patients with psoriasis has not yet been studied in detail.[4 5] Recurrence risk and segregation analysis on families with psoriasis report a recurrence risk ratio in first-degree relatives (λ_{FDR}) of about 8, thus indicating that psoriasis is mostly genetic, but that the genetic background is multifactorial and heterogeneous.[6] Family studies on psoriatic arthritis (PsA) have provided prevalence estimates among first-degree relatives ranging between 2.1 and 8.3%[7–12] corresponding to a recurrence risk ratio (λ_{FDR}) between 14 and 55 assuming a PsA prevalence at 0.15%. However, because PsA classification requires the presence of psoriasis, the λ_{FDR} for PsA should only be calculated on pairs of relatives concordant for psoriasis. Consequently, λ_{FDR} for peripheral and axial arthritis in first-degree relatives with psoriasis was about 3.5 assuming a 10% prevalence of arthritis in patients with psoriasis.[13–17]

Molecular genetic studies have indicated that regions at chromosome 6p and 16q are linked to PsA.[18 19] Associations independent of psoriasis have been reported in the major histocompatibility complex region at HLA-DRB1, DR4, DR7, B13, B16 (B38+B39), B17 (B57) and B27.[6 20 21] However, all these associations were in linkage disequilibrium with HLA-Cw0602. Because of the linkage of PsA to chromosome 16q it has been investigated whether PsA is associated with CARD15 (NOD2) polymorphisms but this has yielded divergent results.[22–24] Hence, at the present time the genetics of PsA are largely unresolved.

In the absence of previous studies of twins with PsA, we performed a nationwide study among unselected twins in Denmark to estimate the relative significance of genetic and environmental effects in the development of PsA.

METHODS

Ascertainment of twins

The study comprised three nationwide twin populations, which were contacted on two occasions. In 1994, a cohort born 1920–40 including 1631 same-sexed twin pairs and a cohort born 1953–82 including 20 131 same and opposite sexed twin pairs were invited to participate in a nationwide twin survey.[25] A total of 37 388 twin individuals responded to this first survey. In 2002, 17 918 twin individuals from the 1930–52 cohort and in addition 28 500 twin individuals from the 1953–82 cohort were invited to participate in a follow-up survey.[26] Questions on rheumatic diseases were identical in the two surveys, including a question on PsA asking if the recipient had ever suffered from PsA.

Validation of self-reported psoriatic arthritis

Twins reporting PsA in either the 1994 or the 2002 survey received a clinical profile questionnaire followed by a telephone interview. Twins with possible or definite PsA were asked for permission to address their non-affected co-twin. If the twins agreed to participate they underwent a structured interview, clinical examination, and blood samples were drawn for measurement of IgM rheumatoid factor, HLA-B typing and zygosity determination on DNA. We collected available medical records to obtain information about arthritis or psoriatic skin disease in the past. The Moll and Wright (M&W)[27]

and the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria[28] were adopted for the classification of PsA. Psoriasis and arthritis were only accepted if observed by the investigator or documented in medical records from dermatologists or rheumatologists. Time of onset was defined as the self-reported onset of joint disease and psoriasis respectively. Discordance time was defined as the time from first onset of symptoms in one twin to onset in the second twin or end of observation. Time of shared environment was defined as number of years that twin individuals had lived together.

Validation of completeness

To identify non-responding twins with PsA or responding twins who failed to report PsA we made a record linkage with the Danish National Patient Registry.

Ethics

All the regional scientific ethics committees in Denmark and the Danish data protection board approved the study.

Analysis

The classical twin method was used to estimate the risk of a twin to acquire PsA by using probandwise concordance rates, which is the same as the casewise concordance rate corrected for incomplete ascertainment.[29 30] A proband was defined as a twin who independently of the co-twin reported PsA and who fulfilled the classification criteria. A secondary case was a twin ascertained through a co-twin fulfilling the same criteria. Only pairs in which one or both twins fulfilled the proband criterion were included. The statistical strength of the study was estimated by pairwise concordance rates testing the null hypothesis (concordance rate in monozygotic (MZ) twins = concordance rate in dizygotic (DZ) twins) against the alternative hypothesis by Fisher's exact test. The genetic effect was assessed using family risk ratios. Familial aggregation was indicated if the recurrence risk ratio in MZ (λ_M) and DZ (λ_D) twins was more than 1.[31 32]

Tetrachoric correlations (r) and the determination of best-fit model for the heritability of the disease were conducted using a structural equation modelling in the Mx software program.[33] In order to allow calculation on categorical variables this method introduces a liability model, which assumes that the dichotomous distribution of the trait (affected versus non-affected) reflects an underlying, normally distributed likelihood of having the condition. The threshold value reflects the prevalence of the trait. Structural equation modelling quantifies sources of individual variation by separation of the observed phenotypic variance into additive genetic effects (A), dominance genetic effects (D), common environmental effects (C) and random environmental effects (E). Heritability is defined as the proportion of the total phenotypic variance that is attributable to genetic variance (A+D). Tetrachoric correlations are used to decide which aetiology model has the best fit. In terms of additive genetic (V_A) and dominance genetic (V_D) variances, the expected tetrachoric correlations between MZ and DZ pairs are $rMZ = V_A + V_D$ and $rDZ = 0.5\ V_A + 0.25\ V_D$ respectively. The selection of the best-fit model is based on goodness-of-fit. The variance component model requires that the trait is polygenic with no major genes involved, and that A+D+C+E = 1.

RESULTS

The overall response rates after one reminder were 81.5% (31 629 of 37 388) and 75.3% (34 944 of 46 418) in the 1994 and the 2002 Danish Twins Surveys respectively. PsA was reported by 233 (54 MZ and 179 DZ) twin individuals. The steps in the recruitment and validation process are shown in fig 1. The response rate to the subsequent invitation to validate the diagnosis was 70%. Among the 163 responders, 32 (20%) reported that they did not have PsA or declined further participation in the study. In 89 twin-responders the diagnosis could not be rejected by telephone interview or information from medical records. They underwent clinical examination and interview to ensure an optimally validated diagnosis. Fifty-one probands (12 MZ and 39 DZ) with self-reported PsA fulfilled the criteria by M&W. Forty-six probands fulfilled the CASPAR criteria. Among the pairs fulfilling the M&W or the CASPAR criteria, 36 and 31 co-twins respectively were included. One MZ and one DZ co-twin were identified as secondary PsA cases.

The zygosity distribution was almost equal in responders and non-responders (MZ proportion responders 38 of 164 = 0.23, MZ proportion non-responders 19 of 64 = 0.30, difference 0.07 (95% CI: −0.06, 0.20). Among the responders, there was no difference in response rate between MZ and DZ pairs (71.7% and 71.4% respectively) and no differences between MZ and DZ twins with PsA with respect to age, sex, age at onset of psoriasis, onset of arthritis, discordance time, time of shared environment, arthritis pattern, HLA-B27 or HLA-B13 prevalence (table 1). With regard to axial disease, 16 probands complained of inflammatory back pain and 11 of those had *x*-rays of sacroiliac joints taken (69%). Five twins had definite sacroiliitis on *x*-ray (two MZ and three DZ).

The record linkage to the National Patient Registry did not identify additional concordant twin pairs.

Concordance estimates

According to the M&W criteria, the probandwise concordance rates were 1/10 (10% (95% CI: 2%, 40%)) and 1/26 (3.8% (95% CI: 0.7%, 19%)) in MZ and DZ twins respectively (difference 6.3% (95% CI: −11%, 37%), p = 0.49) (table 2). If the CASPAR criteria was used, the probandwise concordance rates were 1/9 (11% (95%CI: 2%, 44%) and 1/22 (5% (95% CI: 1%, 22%) in MZ and DZ twins respectively (difference 6.6% (95%CI: −13%, 39), p = 0.52) (table 2).

With regard to psoriasis skin disease in the PsA population (defined by the M&W criteria), the probandwise concordance rates were 6/11 (55%) in MZ twins and 6/28 (21%) in DZ twins (table 2). Testing the null hypothesis against the alternative hypothesis on psoriasis based on pairwise concordance rates using Fisher's exact test yielded significantly higher concordance rates among MZ than DZ twin pairs (difference 34% (95% CI: 2%, 60%), p<0.05). Thus, based on concordance estimates, we found a significant genetic effect on psoriasis skin disease in twins with PsA.

The probandwise concordance for arthritis in MZ and DZ pairs concordant for psoriasis were 1/6 and 1/6 respectively. Thus, our data indicate that the different occurrence of PsA in MZ and DZ twins reflects the different concordance rates for psoriatic skin disease in MZ and DZ twin pairs with PsA. This is also suggested by the almost equal R_{MD} in psoriasis and PsA.

To assess the possible information bias arising from all twins being examined by the same investigator and bias arising from comparing genetically heterogeneous twin pairs or phenocopies the concordance rates were also calculated among disease subsets. A total of two MZ and eight DZ twins presented with PsA at clinical examination only. By exclusion of these twins from the analysis and adopting the M&W criteria, the probandwise

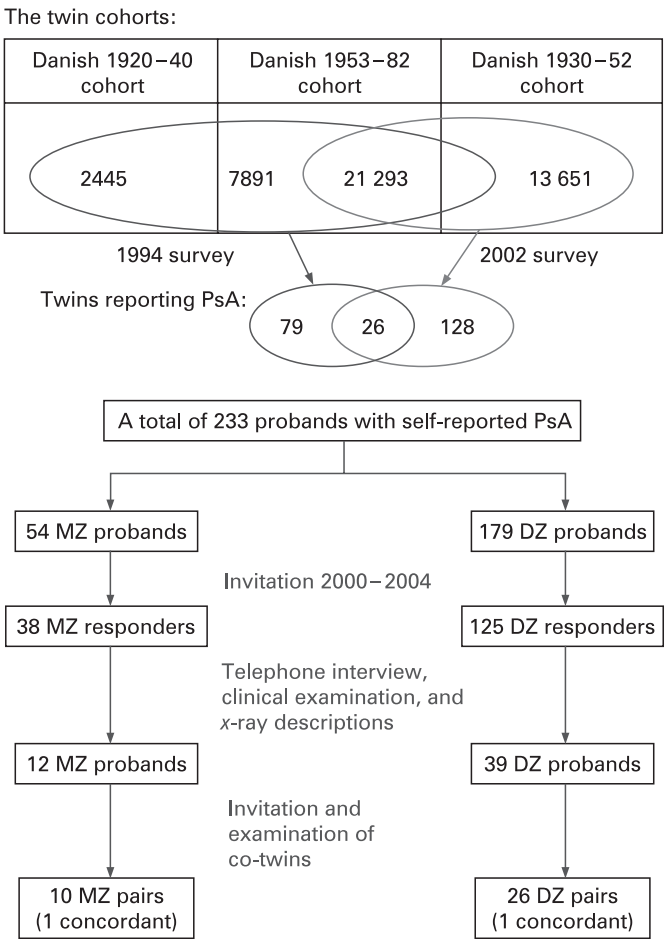

Figure 1 Validation of self-reported psoriatic arthritis (PsA). Data based on the Moll and Wright criteria. MZ, monozygotic; DZ, dizygotic.

concordance rate in MZ and DZ twins were 11% and 4.8% (difference 5.8% (95% CI: −15.6%, 38.5%), NS). Thus, exclusion of this potential source of information bias did not substantially change the concordance estimates in MZ and DZ twins.

It has been proposed that there are two types of psoriasis and PsA: a familial form of early onset (type I) and a late onset sporadic form (type II).[6 34–36] By inclusion of twins with onset of psoriasis before the age of 30 only, we identified five MZ pairs of which one was concordant, and 18 DZ pairs of which one was concordant. This 14% difference in proportions did not reach statistical significance (95% CI: −12%, 57%, NS). Regarding onset of PsA before the age of 30, we identified three MZ twins of which one was concordant and eight DZ pairs, which were all disease discordant. The 33% difference was not statistically significant.

Recurrence risk

Based on a PsA prevalence of 0.15% and the probandwise concordance rate among DZ twins the recurrence risk ratio (λ_D) was estimated to be 25.6, confirming previous reports of familial aggregation.[7–12] The MZ:DZ ratio defined by R_{MD} $[(\lambda_M-1)/(\lambda_D-1)]$ was 2.7 (95% CI: 3.3, 204). The R_{MD} for psoriasis in twin pairs with PsA was 2.8 (95% CI: 0.7, 9.9).

Variance component analysis

Statistical modelling of data in Mx indicated that a dominance genetic effect was negligible (tetrachoric correlation MZ = 0.68 and tetrachoric correlation DZ = 0.52).[33] and the data did not favour any specific model (A, additive genetic effects; C, common environmental effects; and E, random environmental effects) of inheritance of PsA (AE: χ^2 (2 df) = 0.70, p = 0.87, CE: χ^2 (2 df) = 0.41, p = 0.94, and ACE: χ^2 (1 df) = 0.00, p = 1.00). Supposing that genes and environment both contribute to the development of PsA we calculated an additive genetic effect of 34% (95% CI: 0%, 92%) and a common environmental effect of 35% (95% CI: 0%, 78%) on the variance in the causation of PsA. Of note, however, based on variance component models in Mx, our study did not appear to be adequately powered to provide unequivocal evidence on the contribution of genes in PsA pathogenesis.

In psoriasis the fit of the common environment and random environment (CE) model fails (χ^2 (2 df) = 3.79, p = 0.29), whereas the fit of additive genetic effects and random environment (AE) model was better (χ^2 (2 df) = 0.73, p = 0.87) suggesting the involvement of additive genetic effects in the causation of psoriasis. From the AE and the ACE model, the additive genetic effect on psoriasis would range between 92% (95% CI: 73%, 98%) and 63% (95% CI: 0%, 75%).

Table 1 Distribution of demographic and clinical characteristics according to zygosity in a nationwide Danish population of twins with PsA (Moll and Wright criteria)

Characteristics of PsA cases	Monozygotic (n = 12)	Dizygotic (n = 39)	Difference (95% CI)
Pairwise characteristics			
Mean age in 2002 in years (range)	50 (27, 74)	51 (27, 79)	1.0 (−6.3, 8.4)
Mean discordance time of arthritis (range)*	8.7 (1, 16)	13 (1, 42)	4.4 (−2.2, 11)
Mean time of shared environment (range)*	19.0 (14, 30)	19 (14, 29)	0.7 (−0.8, 2.2)
Characteristics of twin individuals			
Female proportion	29%	52%	24% (−6%, 46%)
Mean age at onset of psoriasis (range)	29 (11, 50)	26 (2, 54)	3 (−5.5, 11)
Mean age at onset of arthritis (range)	37 (20, 59)	36 (18, 63)	0 (−8, 8)
Mean number of joints involved†	4.5	3.7	0.9 (−1.1, 2.9)
Proportion with axial disease‡	17%	7%	9% (−8%, 38%)
Proportion with nail involvement	71%	50%	21% (−8%, 44%)
Proportion HLA-B13 positive	0%	11%	11% (−12%, 25%)
Proportion HLA-B27 positive	21%	5%	16% (−3%, 42%)

PsA, psoriatic arthritis.
*Calculated on the pairs that were concordant for response. †Number of joints with current or previous arthritis. ‡Axial disease was defined as inflammatory back pain and definite unilateral or bilateral sacroiliitis on *x* ray (see text).

DISCUSSION

This is the first twin study conducted on PsA. In psoriatic skin disease a genetic predisposition was confirmed. The almost identical concordance rates for PsA among MZ and DZ twins

Table 2 Probandwise concordance estimates on psoriasis and PsA

PsA	Monozygotic twins	Dizygotic twins	Difference (95% CI), p*
Moll and Wright criteria	1/10 (10%)	1/26 (3.7%)	6.3% (−11%, 34%)
CASPAR criteria	1/9 (11%)	1/22 (4.5%)	6.6% (−12%, 39%)
Psoriatic skin disease in twins with PsA	6/11 (55%)	6/28 (21%)	34% (2%, 60%), p<0.05

PsA, psoriatic arthritis.
*p Value estimated using Fisher's exact test on the pairwise concordance estimates.

suggest that the genetic contribution to psoriasis-related joint disease is less prominent. However, despite this difference between psoriasis skin and joint disease the statistical power of our study does not allow us to draw definite conclusions regarding the quantitative participation of previously proposed genetic effectors on PsA.

Dividing the population of twins with PsA into subgroups indicated that the genetic influence on PsA development may differ in separate disease subsets. Thus, the higher concordance in MZ twins with onset of disease before the age of 30 support this impression. However, these estimates did not differ significantly and conclusions based on information on disease duration could be influenced by recall bias.

The external validity of the present findings is strengthened by the population-based twin ascertainment procedure, by the fact that we did not identify additional concordant twin pairs by record linkage to the National Patient Registry, and by the occurrence findings on PsA in this Danish twin population, which are equivalent to other studies (unpublished data). Furthermore, we found a higher concordance rate for psoriasis in MZ as compared with DZ twin pairs ($p<0.05$), and an increased recurrence risk for PsA and psoriasis in DZ twins comparable with the recurrence risk in first-degree relatives reported by Moll and Wright.[10]

However, several issues should be considered when interpreting these findings.

Epidemiological studies on PsA are hampered by the lack of an internationally accepted case definition for PsA based on a ''gold standard''. We adopted the classification criteria by M&W in addition to the newly proposed CASPAR criteria.[27 28] The use of these different criteria did not change the overall result of the study.

In the present setting, information bias may arise from the same investigator examining the whole cohort, bias caused by different amounts of diagnostic information available among MZ and DZ twins, and bias due to the misclassification of PsA. The diagnosis of PsA could be established without data from medical files if the twin had psoriasis and arthritis at the time of examination, which was the case in 10 probands. In such cases, bias could be introduced, if the clinical judgement by the investigator was influenced by knowledge about the zygosity status. To study this potential source of bias, concordance rates were calculated on twins with the diagnosis derived from medical records only. This approach, however, did not change the concordance estimates between MZ and DZ twins. Even if there may have been qualitative or quantitative differences between MZ and DZ twins with respect to the information available from medical files, this problem was conceivably small because all twin individuals underwent an identical structured interview and clinical examination. Data from medical records were available for all probands except for two DZ twin pairs. Thus, the risk of information bias would appear to be negligible.

By comparing MZ and DZ twins with PsA no differences were observed with regard to potential disease modifiers, including age, sex, discordance time, time of shared environment and HLA-B types. The discordance time of pairs with PsA in this study was slightly higher in DZ as compared with MZ twins. As the peak age at onset of PsA occurs in the fourth and fifth decade we cannot be certain, that the discordant pairs may eventually become concordant. However, the problem concerning discordance in younger age segments is similar among MZ and DZ twins. Thus it is unlikely, that the discordance time has influenced the concordance figures of this study.

In conclusion, bearing in mind that the presence of one disease (arthritis) within another (psoriasis) may modify the clinical expression of either condition, the present nationwide twin study demonstrates that psoriatic skin disease has a genetic background; however, the role of genes for the development of psoriasis-associated peripheral arthritis is less clear. Future twin studies with improved power are warranted to explore in further detail the possible differential effect of genes and environment in the causation of psoriatic skin disease and PsA.

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