A strong heritability of psoriatic arthritis over four generations—the Reykjavik Psoriatic Arthritis Study

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Objective. We have studied the prevalence of PsA in Reykjavik, Iceland, in a population-based cohort, and using the Icelandic genealogy database we have estimated the risk ratio (RR) spanning five generations.

Methods. The national identification numbers of all 220 living Icelanders in Reykjavik known to have PsA were linked with the genealogy database. RRs for developing PsA were estimated in first-degree relatives (FDRs) to fifth-degree relatives of PsA cases. The kinship coefficient (KC) for PsA was also calculated. The control populations were 1000 and 10 000 sets of matched Icelandic subjects for each proband, respectively.

Results. FDRs to fourth-degree relatives of patients with PsA had RRs of 39, 12, 3.6 and 2.3, respectively (all \( P\)-values < 0.0001), reflecting a strong genetic component, whereas the fifth-degree relatives had an RR of 1.2 (\( P = 0.236\)). KCs of 5.0, 3.4, 1.7, 1.3, 1.0, 0.8 and 0.7 were observed for the first seven excluded meioses (all \( P\)-values < 0.0001), confirming the familial risk.

Conclusions. Patients with PsA in Reykjavik, Iceland, are significantly more related to each other than to randomly sampled control subjects. This is in agreement with previous reports, but the present study examines the inheritance in more distantly related individuals. These findings indicate that in addition to a strong and complex genetic component in PsA, there is an important environmental contribution.

Key words: Genealogy database, Heritability, Psoriatic arthritis, Familial, Genetic.

Introduction

PsA is an inflammatory joint disease associated with psoriasis, usually RF negative, and is an entity separate from RA [1]. In 1973, Moll and Wright [2] proposed diagnostic criteria that have been used by most researchers. However, recently, the classification criteria for psoriatic arthritis (CASPAR) group published classification criteria that were clinically validated in established disease for use in research settings [3], whereas a Swedish group suggested criteria for use in clinical settings, including in early disease [4]. Although PsA is found primarily in those with the skin disease psoriasis, PsA sine psoriasis is well described and diagnosed by rheumatologists [5], and the CASPAR criteria do not require the skin disease psoriasis to be present for the diagnosis to be made [3]. PsA should therefore not be sought only among patients with the diagnosis of psoriasis as cases without psoriasis will be missed, as well as cases where the skin disease is mild and has not been diagnosed or treated separately.

Population-based prevalence studies from the Nordic countries and Canada suggest that the prevalence of PsA is between 0.16 and 0.20% [6], and we have recently published the prevalence in Reykjavik, Iceland, based on Swedish criteria, and found it to be close to 0.16% [7]. Clinicians are well aware of the heritability of the skin disorder psoriasis as well as of PsA among first-degree relatives (FDRs), an observation that has been confirmed in a number of studies [8–12].

Moll and Wright [13] presented several pedigrees in 1973, which illustrated the presence of significant familiarity in PsA. In their report, they described a pair of triples (Pedigree No. 9), who had a mother with a SpA and a father with psoriasis and SpA with peripheral arthritis. Two out of these triples were identical twins, and both had PsA, but with a different subcategory of arthritis, whereas the third triple were without any sign of joint or skin disease. Not until recently was there a twin study focusing solely on the heritability of PsA. The report by Pedersen et al. [14] demonstrated in a cohort of around 33 000 Danish twins that the prevalence of PsA in Denmark was 0.15%, similar to what we found in Reykjavik [7], and they also reported that the concordance rate between monozygotic twins was only 10–11%, independently of whether they used the classification criteria by Moll and Wright from 1973 [2] or the more recent CASPAR criteria [3].

Several studies have evaluated the heritability of PsA among FDRs of cases with PsA [8–12, 15, 16]. These studies illustrate that FDRs have a significantly elevated risk of having PsA, with a sibling recurrence risk ratio (RR) (lambda; \( \lambda_S \)) of 14–55, where \( \lambda_S \) is defined as the prevalence of disease in relatives of affected index cases divided by the prevalence in the general population. However, previous studies of the heritability of PsA have had various limitations, including limited cohort size, in most cases excluding relatives beyond FDRs, use of index patients from specialty clinics, and the ascertainment bias of looking for FDR cases within a family after identifying the index case, which can result in inflated \( \lambda_S \) values, as suggested by Sun-Wei Guo [17]. Finally, in no previous study was the population prevalence of PsA known, resulting in a \( \lambda_S \) based in large part on a subjective estimate. To overcome some of these methodological problems we have recently identified all known cases with PsA in the area of Reykjavik, Iceland [7]. Furthermore, by using the genealogical database run by deCODE Genetics in Iceland we have been able to calculate the RR for family members in several generations of individuals with PsA.

Materials and methods

The Reykjavik Psoriatic Study Group

The present study includes patients living in the Reykjavik area of Iceland diagnosed with PsA by rheumatologists. The adult population of the Reykjavik area, where 63% of the adult population of the country resides, numbered 134 253 at the time of this study. Patients were recruited from two sources.

First, from a database of 1386 patients with verified psoriasis created during ongoing studies of psoriasis [18, 19]. This database contains information on ~1% of the Reykjavik population and its recruitment sources included all affected members of the
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Icelandic Psoriasis Foundation (SPOEX) and all family members of these patients, regardless of whether they were reported to have psoriasis or not, and patients recruited through a publicity campaign. Patients who had only psoriasis were excluded. From this database, 152 individuals who lived in the Reykjavik area in 2003 and reported that they had been diagnosed with PsA by a rheumatologist were included in the present study.

Secondly, to recruit patients beyond those known to have psoriasis, another source of recruitment was an electronic registry of patients admitted to the Landspítali-University Hospital (LUH) between 1981 and 2001. LUH serves as a primary hospital for Reykjavik and its suburbs, and it is the only secondary and tertiary care hospital in Iceland. This source yielded 98 patients.

These two databases were used to identify patients with different disease characteristics, based on our expectation that the psoriasis database does not include all patients with psoriasis, and is likely to miss patients with mild skin disease and arthritis. It was therefore expected that the two sources would not overlap to a great degree, and accordingly only 30 patients were present in both. Therefore, they jointly provided 220 patients who had been diagnosed with PsA by a rheumatologist [7].

These rheumatologist diagnoses, some of which were self reported, were validated by inviting all 220 patients to participate in our study, and eventually 156, or 71%, were interviewed and examined. We confirmed PsA in 131, or 84%, using a set of previously published criteria [4]. Since our study was done before the publication of the CASPAR criteria, we may have excluded patients with PsA sine psoriasis, and being a cross-sectional study we may also have excluded real cases of PsA that did not have verifiable disease at the time of their visit. Thus, having found that the disease could be independently validated in at least 84% of the cases, and as the inclusion of patients without disease biases our results towards the null, we included all 220 patients in our analysis.

Genealogy database
deCODE Genetics (Reykjavik, Iceland) has built a computerized genealogy database of more than 760,000 individuals [20]. The database contains records of all living Icelanders comprising more than 300,000 individuals, and a large proportion of all individuals of Icelandic descent who have ever lived in the country as well. The genealogy of the entered individuals is recorded from multiple sources, including church records, censuses from previous centuries, and, more recently, published genealogies. The genealogy database is essentially complete from the 18th century to the current time, thus allowing distant relationships to be traced accurately [21].

Use of this database allows investigation into the relationships among patients with PsA, as well as assessment of the various levels of relatedness. It also allows the creation of matched control groups for use in assessing the statistical significance of the results. To ensure anonymity of the patients in the present study, the social security numbers of participants were sent to the Data Protection Commission of Iceland for encryption before arriving at the laboratory [22]. Thus, all medical information was imported to deCODE Genetics with encrypted identifiers.Both the Icelandic National Bioethics Committee and The Icelandic Data Protection Authority approved the study for the Reykjavik PsA Study.

Assessment of inheritance

The RR for disease in relatives is a measure of the risk of disease in a relative of an affected person as compared with the risk in the population as a whole. Obtaining valid estimates of the RR is, however, not straightforward, because many sampling schemes may lead to biased or inaccurate estimates [17]. The use of a population-based group of patients eliminates some of this potential sampling bias. In addition, a near-complete genealogy database facilitates identification of patients who are related to other patients. It is important to note that only probands were used in our analysis, and no attempt was made to recruit relatives of cases of PsA. This design avoids the potential overestimation of familiarity when secondary cases are recruited through probands, as described by Sun-Wei Guo [17].

Kinship coefficients

We incorporate a kinship coefficient (KC), a measure of identical-by-descent sharing, to assess whether the affected individuals are more related than a set of matched controls. The KC for a pair of individuals is the probability that, for a particular autosomal locus, two randomly selected alleles, one from each individual, are inherited from a common ancestor [23]. We determined the mean pair-wise KC for the set of PsA patients and compared this with the distribution of the mean pair-wise KC for 10,000 sets of matched controls. Each patient was matched to a single control individual in each control group. The controls were drawn at random from the genealogical database and were matched on the year of birth, gender and the number of ancestors recorded in the genealogy database. Because of the large size of the pedigrees, there was a computational problem in accurately determining the KC. Monte Carlo simulations were used to approximate the average pair-wise KC for each group. A total of 100,000 simulations were performed to ensure that the Monte Carlo errors had a negligible effect on the results. Empirical P-values were calculated by counting how many sets of controls had average pair-wise KCs larger than the set of affecteds being tested. The contribution of close relatives dominates the KC values. To show that increased relatedness extends beyond FDRs, the results of KC calculations were refined by excluding the genetic contributions from relatives at one or two meioses, up to and including seven meioses. The KC is expressed as a genealogical index of familiarity, calculated as the mean KC—10,000 [24]. All P-values reported are nominal.

RR

To assess the significance of the RR obtained for a given group of patients, we compared their observed values with the RR computed for up to 1000 independently drawn and matched groups of control individuals [25]. The control individuals were selected in the same manner as described above for the KC calculations. Empirical P-values can be calculated using the control groups; thus, a P-value of 0.05 for the RR would indicate that 5% of the matched control groups had values as large as or larger than that for the patient’s relatives or spouses. The number of control groups required to obtain a fixed accuracy of the empirical P-values is inversely proportional to the P-value. We therefore selected the number of control groups generated adaptively up to a maximum of 1000. When none of the values computed for the maximum number of control groups was larger than the observed value for the patient’s relatives and mates, we report the P-value as being <0.001. Using a variance stabilizing square-root transform, an approximate CI may be constructed based on the distribution of RR for control groups.

Results

Pedigrees

Figure 1 shows an example of a pedigree with 17 patients with PsA (in blue) and five patients with only psoriasis skin disease (in black) in one family. In some families, six patients were related within and at a distance of only six meioses. The pedigrees demonstrated significant clustering of patients with PsA. Additional pedigrees can be obtained from the authors on request.

RRs in relatives

The RR estimates for disease in relatives of affected patients with PsA are shown in Table 1. The RRs for PsA were 39.2, 12.2, 3.6
and 2.6 (all \( P \)-values < 0.0001) among FDRs, second-degree relatives (SDRs), third- and fourth-degree relatives of affected patients, respectively. The RR for the fifth-degree relatives did not reach significant levels (RR 1.2; \( P = 0.236 \)).

### Sex differences

Calculation of the RR for PsA in relatives of affected patients with PsA in relation to the sex of the index case demonstrated a higher RR if the proband was a male patient in both first and third generations; 41.1 vs 37.8 (\( P = 0.95 \)) and 4.9 vs 2.8 (\( P = 0.42 \)). Meanwhile, it was higher in the fourth generation when the index case was a female patient (3.0 vs 1.9; \( P = 0.42 \)). No differences in the RR in SDRs were observed with regard to sex, with 12.3 in the male vs 12.2 in the female index case (\( P = 1 \)). Thus, these differences in respect to the sex of the index cases did not reach statistical significance.

### RRs in spouses

As no spouse of a patient in our study had PsA, we are unable to calculate a meaningful RR for this group. Furthermore, only three spouses had psoriasis in this group, or 1.2%, thus similar to the background population.

### KCs

**Figure 2** shows the relatedness of patients with PsA. On the basis of the KC, it was evident that patients with PsA were significantly more related to each other than were population controls. The KC was significantly higher in cases than controls up to seven meioses apart. Calculation of the KCs confirmed these patterns of familial risk with significantly elevated KC values of 5.0, 3.4, 1.7, 1.3, 1.0, 0.8 and 0.7 for the first seven excluded meioses (all \( P \)-values < 0.0001).

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**Table 1.** RR estimates of PsA in relatives in five generations of affected individuals with verified PsA

<table>
<thead>
<tr>
<th>The degree of relationship</th>
<th>RR</th>
<th>( P )-value*</th>
<th>No. of affected relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDRs</td>
<td>39.2</td>
<td>&lt;0.0001</td>
<td>1.52</td>
</tr>
<tr>
<td>SDRs</td>
<td>12.2</td>
<td>&lt;0.0001</td>
<td>2.58</td>
</tr>
<tr>
<td>Third-degree relatives</td>
<td>3.6</td>
<td>&lt;0.0001</td>
<td>7.89</td>
</tr>
<tr>
<td>Fourth-degree relatives</td>
<td>2.6</td>
<td>&lt;0.0001</td>
<td>16.69</td>
</tr>
<tr>
<td>Fifth-degree relatives</td>
<td>1.2</td>
<td>0.236</td>
<td>38.56</td>
</tr>
</tbody>
</table>

Risk estimates for PsA are the RR (95% CI) for the estimated risk of having the disease itself (e.g., the risk of PsA in a relative of a patient with PsA) as compared with the risk in 10,000 sets of Icelandic control subjects. *\( P \)-values are one sided and indicate the significance of the risk of disease in the combined relative groupings of all generational levels as compared with matched control subjects.
Discussion

The present study, consisting of an unselected group of all known patients with PsA in the greater Reykjavik area of Iceland, evaluated for relationships in an extensive genealogical database in Iceland, demonstrates a strong heritability of PsA over several generations. The results presented here are the first to illustrate significant familiality of PsA over four generations.

This study confirms previous studies of the heritability of PsA that have shown an effect among FDRs [8–13, 16]. All of those studies illustrated a high risk of disease in both siblings and other FDRs of individuals with PsA, with a \( \lambda_S \) of up to 55 [25]. Unless large control groups are used, as we present here, the calculation of a \( \lambda_S \) value is dependent on knowing the underlying population prevalence as this is the denominator of the RR calculation. All previous studies relied on estimates of the population prevalence as it was unknown in the populations studied. Therefore, the findings require confirmation in a population where the prevalence is known and published, such as in the Reykjavik area. Here, we used methods that do not make direct use of the prevalence value of PsA in the background population, but do rely on having located all known cases in the underlying population, as we did in our recent population-based study on the prevalence of PsA in Reykjavik [7]. Having identified all known cases of PsA in the study population, and by using an extended genealogical database, we were able to calculate the RR of suffering from the studied condition, i.e. PsA, in siblings, other FDRs and other relatives over five generations as compared with the population in general. This is the major strength of our study.

Having a complete patient list linked to the genealogy database ensures that all patients and relatives of patients are included in the study. This assumes that ascertainment is complete and the results are reliant on that fact. In the case of the data presented here, we have used the same list as the basis for a previous publication on the prevalence of PsA in Reykjavik area of Iceland [7]. Our recruitment strategy relied on using two complementary data sources to reach patients who we expected to miss if we used only one method due to the varying degree of skin symptoms associated with PsA. The prevalence figures we obtained coincide remarkably well with published numbers for other Scandinavian countries, suggesting that our assumption of complete ascertainment is robust.

It is important to note that the psoriasis database we used to locate cases of PsA is not complete, and cannot be used for assessment of familiality of the skin disease. Alone, it suggests a prevalence of 1.0% for psoriasis, whereas we expected it to be \( \sim 1.4\% \) based on the experience in Norway [26]. As part of our evaluation of the completeness of our ascertainment of PsA, we used the prevalence of arthritis in the psoriasis database to estimate how many patients with psoriasis would be needed to give rise to the 68 cases of PsA we observed outside the psoriasis database. This analysis suggests that the prevalence of psoriasis in Reykjavik, Iceland, based on our PsA data is 1.4\%, exactly matching that reported for Norway. This analysis further supports our claim that the ascertainment of PsA is complete.

Our findings of an increased RR for PsA of 40 in FDRs of individuals with this joint disease are comparable with previous reports [8–13, 16]. Only one previous study has reported on PsA in SDRs in a cohort of 88 patients with PsA, where barely 66% of the SDRs, or 43 individuals, accepted participation, and only one of those had PsA [13]. In our study, we identified all known PsA cases in the study area and all of their relatives using existing databases. Therefore, the results are neither dependent on clinical evaluation of all the relatives of our arthritis patients nor on the prevalence value of the condition in the study area, which improves the validity of our results. We found significantly increased RRs for having PsA, not only among FDRs but also in SDRs, and third- and fourth-degree relatives. Not until in the fifth-degree relatives did this risk mostly disappear, although a trend was still detectable with an RR of 1.2 \((P=0.236)\).

The observation of an RR of 40 and 12 for FDRs and SDRs, respectively, of PsA patients to develop the same condition is far higher than those that has been observed using the same methods for RA in Iceland or 4.38 (95% CI 3.26, 5.67) for FDRs and 1.95 (95% CI 1.52, 2.43) for SDRs [27] and others have reported a \( \lambda_S \) value of 8 for FDRs of patients with RA [28]. On the other hand, much stronger heritability has been reported for AS (\( \lambda_S \) 50–82) [29, 30].

Some studies indicate that there may be differences in the heritability of PsA depending on whether the proband is male or female, e.g. results from a genome-wide linkage study of 1000 individuals with psoriasis stratified by arthritis status demonstrated higher paternal than maternal transmission on chromosome 16; logarithm of the odds (LOD) 5.69 \( \text{vs} \) 2.9 [31, 32]. Although we found some differences in RR between genders, they were neither constant between generations nor statistically significant.

The pathogenesis of psoriasis and PsA is unknown to date, but the present results demonstrate that genetic factors play a strong role in the development of PsA and that this effect extends over several generations. Our study was not designed to elucidate any shared environmental or immunological factors that may play a role in the pathogenetic processes of PsA. Further prospective studies are necessary to elucidate such susceptibility factors. However, our findings help illustrate the complex relationship between genes and environment in the pathogenesis of PsA. This may explain why large genetic studies on these subjects, both linkage studies and genome-wide scans, have not been able to discover any gene with a major impact on the development of PsA outside of the HLA loci.

In conclusion, patients with PsA in Reykjavik, Iceland, are significantly more related to each other than to a random sample of Icelandic subjects. This is in agreement with previous reports on the heritability of PsA, but the present study examines the inheritance in more distantly related individuals than previous studies. The RRs of the SDRs of probands are sufficiently less than those of FDRs, and those of third-degree relatives less than those of SDRs, suggesting that in addition to a strong genetic component there is a strong environmental component to the risk, given that more distant relatives are less likely to share an environment. These findings underline the strong and complex nature of the genetic component of PsA. They also demonstrate the benefits of using all index cases in a geographical location.

Rheumatology key messages

- Patients with PsA are related over several generations.
- There are strong genetic and environmental contributions to PsA.
- Linking all known cases to a genealogical database helps overcome some methodological limitations.

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