

BRIEF REPORT

Impact of Having Family History of Psoriasis or Psoriatic Arthritis on Psoriatic Disease

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Objective. Psoriatic arthritis (PsA) has a genetic background. Approximately 40% of patients with psoriasis or PsA have a family history of psoriasis or PsA, which may affect disease features. The aim of this study was to assess the effects of family history of psoriasis and PsA on disease phenotypes.

Methods. Data from 1,393 patients recruited in the longitudinal, multicenter Psoriatic Arthritis International Database were analyzed. The effects of family history of psoriasis and/or PsA on characteristics of psoriasis and PsA were investigated using logistic regression.

Results. A total of 444 patients (31.9%) had a family history of psoriasis and/or PsA. These patients were more frequently women, had earlier onset of psoriasis, more frequent nail disease, enthesitis, and deformities, and less frequently achieved minimal disease activity. Among 444 patients, 335 only had psoriasis in their family, 74 had PsA, and 35 patients were not certain about having PsA and psoriasis in their family, so they were excluded from further analysis. In the multivariate analysis, family history of psoriasis was associated with younger age at onset of psoriasis (odds ratio [OR] 0.976) and presence of enthesitis (OR 1.931), whereas family history of PsA was associated with lower risk of plaque psoriasis (OR 0.417) and higher risk of deformities (OR 2.557). Family history of PsA versus psoriasis showed increased risk of deformities (OR 2.143) and lower risk of plaque psoriasis (OR 0.324).

Conclusion. Family history of psoriasis and PsA impacts skin phenotypes, musculoskeletal features, and disease severity. The link between family history of psoriasis/PsA and pustular/plaque phenotypes may point to a different genetic background and pathogenic mechanisms in these subsets.

INTRODUCTION

Psoriasis and psoriatic arthritis (PsA) are multidimensional diseases with a strong genetic component. The genetic basis of

psoriasis and PsA is recognized based on family aggregation studies, epidemiologic studies, association studies with human leucocyte antigens, genome-wide linkage scans, and candidate gene studies (1). According to population-based epidemiologic studies,

Supported by the Turkish Society for Rheumatology. Dr. Bakirci's work was supported by the Scientific and Technological Research Council of Turkey and the Turkish Society for Rheumatology.

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Dr. Solmaz has received research support from UCB. Dr. Aydin has received consulting fees, speaking fees, and/or honoraria from UCB, Sanaofi, AbbVie, Janssen, Pfizer (less than \$10,000 each), and Novartis (more than \$10,000). No other disclosures relevant to this article were reported.

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Submitted for publication July 30, 2018; accepted in revised form January 15, 2019.

SIGNIFICANCE & INNOVATIONS

- Psoriasis and psoriatic arthritis (PsA) are diseases that have strong genetic backgrounds. The role of genetics is not only important for the occurrence of the disease but also impacts the phenotype of the patients.
- To date, all studies that have investigated the effect of family history have combined psoriasis and PsA and examined the effect in combination as psoriatic disease.
- Family history of psoriasis and PsA has an impact on skin phenotypes, musculoskeletal features, and disease severity. Family history of PsA versus psoriasis has increased risk of deformities and lower risk of plaque psoriasis.
- The latter is especially of interest because there are well-demonstrated differences in the pathogenesis of plaque versus pustular psoriasis, and the link between family history of psoriasis/PsA and pustular/plaque phenotypes may point to a different genetic background and pathogenic mechanisms in these subsets.

approximately 40% of patients with psoriasis or PsA have a family history of either of these in first-degree relatives (FDRs) (2). Also, for patients with PsA, the recurrence risk ratio (RR) for PsA and psoriasis in FDRs is very high (RR 30–55 for PsA and 4–10 for psoriasis) (3).

Cases of familial versus sporadic PsA have some differences in terms of disease features, such as an earlier age at onset of psoriasis, more frequent nail involvement, and more severe disease in the case of a family history of PsA and/or psoriasis (2).

To the best of our knowledge, studies evaluating the effects of family history have always combined psoriasis and PsA, and the individual effects have not been studied. Because of the genetic differences between psoriasis and PsA as well as the differences between familial and sporadic cases, we hypothesized that family history of psoriasis versus PsA may lead to different disease phenotypes.

PATIENTS AND METHODS

Patient and data collection. The Psoriatic Arthritis International Database is a prospective, multicenter registry for PsA, which was initially developed in Turkey in 2014 and has had the participation of Canada since 2015. Ethics approval was obtained from the local ethics committees (Hacettepe University Ethics Board, Ankara [GO 14/578]; Ottawa Health Science Network Research Ethics Board, Ottawa [20160436-01H]), and all patients gave informed consent prior to data collection. Patients were consecutively registered to the registry with the aim of investigating real-life data using a web-based system (www.trials-network.org). PsA diagnosis was based on the clinical decision of a rheumatologist, and 86.9% of these patients fulfilled the criteria of the Classification

of Psoriatic Arthritis Study Group (4) In this registry, demographics (sex, date of birth, education level, smoking status, weight, height, and calculated body mass index), psoriasis-related data (type, duration, initial site, and nail involvement), and PsA-related data were collected; the details of the collection having been extensively described before (5). Family history was investigated for psoriasis and PsA separately by asking patients the question, “As far as you know, does any member of your family have psoriasis/PsA?” If the answer was affirmative, the relationship of the affected family member with the patient was documented, again, separately for psoriasis and PsA.

Statistical analysis. Descriptive analyses were given using mean \pm SD values for continuous variables and number (percentage) for categorical variables. Either the chi-square test or Fisher's exact test was used to analyze differences between categorical data, while Kruskal-Wallis and Mann-Whitney U tests were applied to test statistical differences between continuous data, as appropriate. We performed logistic regression to determine independent predictors that may be associated with family history of psoriasis or PsA. Plaque psoriasis, nail involvement, presence of enthesitis and joint deformity, age of onset of psoriasis, and sex were included in the final regression model. Due to missing data, minimal disease activity (MDA) could not be included in the final model to calculate MDA status for a large number of patients. SPSS, version 22.0, was used to conduct all statistical analyses.

RESULTS

Effect of family history of psoriasis and/or PsA on disease characteristics. Among 1,393 patients in the database (mean \pm SD age 48 \pm 13.1 years; 63.2% female), 444 patients (31.9%) had a family history of psoriasis or PsA. Patients with a positive family history were more frequently women, had an earlier age at onset of psoriasis, had more frequent nail disease, enthesitis, and presence of deformities, and less frequently achieved MDA (Table 1). On the other hand, no statistical differences were observed for other demographics, clinical characteristics (such as body mass index, arthritis pattern, and number of skin involvement sites), disease activity (measured with the Bath Ankylosing Spondylitis Disease Activity Index), and functional indexes (measured with the Bath Ankylosing Spondylitis Functional Index and Health Assessment Questionnaire). Among patients with a family history of psoriasis or PsA, 320 (72%) had FDRs who had been affected; the rest were second-degree relatives.

Disease characteristics according to family history of psoriasis or PsA. The majority of patients with family history had only psoriasis in their family (335 of 444), while 74 patients had a family history of PsA. A total of 35 patients were not certain about

Table 1. Demographic and clinical features of patients with PsA with or without FH*

	FH of psoriasis or PsA (n = 444)	No FH of psoriasis or PsA (n = 949)	P	FH of PsA (n = 74)	FH of only psoriasis (n = 335)	P
Age, mean ± SD years	48 ± 13.2	48 ± 13.0	0.536	49 ± 13.0	48 ± 13.2	0.370
Sex						0.412
Male	145/444 (32.7)	368/949 (38.8)	0.028†	28/74 (37.8)	106/335 (31.6)	
Female	299/444 (67.3)	581/949 (61.2)		46/74 (62.2)	229/335 (68.4)	
Age at psoriasis onset, mean ± SD years	29 ± 14.8	31 ± 14.9	0.007†	31.9 ± 14.8	28.1 ± 14.4	<0.001†
Age at PsA onset, mean ± SD years	39 ± 13.8	40 ± 13.1	0.450	41 ± 13.4	39 ± 13.6	0.162
BMI, mean ± SD kg/m ²	28.4 ± 5.5	28.0 ± 5.1	0.316	27.8 ± 4.7	28.7 ± 5.8	0.360
Time of psoriasis onset						0.100
Before PsA	348/435 (80.0)	704/937 (75.8)	0.083	50/71 (70.4)	268/329 (81.5)	
Synchronous	77/435 (17.7)	195/937 (20.8)		19/71 (29.6)	53/329 (16.1)	
After PsA	10/435 (2.3)	38/937 (4.1)		2/71 (2.8)	8/329 (2.4)	
Type of skin lesions						0.001†
Plaque psoriasis	221/294 (75.2)	481/665 (72.3)	0.043†	30/52 (57.7)	183/231 (79.6)	
Pustular psoriasis	48/294 (16.3)	147/665 (22.1)		18/52 (34.6)	29/231 (12.6)	
Others	25/294 (8.5)	37/665 (5.6)		4/52 (7.7)	19/231 (8.2)	
No. of skin involvement sites						0.836
<3	287/376 (76.3)	576/773 (74.5)	0.504	49/64 (76.6)	223/296 (75.3)	
≥3	89/376 (23.7)	197/773 (25.5)		15/64 (23.4)	73/296 (24.7)	
Arthritis pattern						
Polyarthritis	186/442 (42.1)	393/945 (41.6)	0.862	37/74 (50.0)	136/334 (40.7)	0.144
Oligoarthritis	169/442 (38.2)	338/945 (35.8)	0.374	23/74 (31.1)	130/334 (39.5)	0.176
Monoarticular	17/442 (3.8)	40/945 (4.2)	0.738	4/74 (5.4)	13/334 (3.9)	0.566
DIP	78/442 (17.6)	165/945 (17.5)	0.932	14/74 (18.9)	58/334 (17.4)	0.751
Arthritis mutilans	2/442 (0.5)	7/945 (0.7)	0.533	0	2/334 (0.6)	0.505
Axial involvement	162/442 (36.7)	330/945 (34.9)	0.530	37/74 (50.0)	136/334 (40.7)	0.108
Joint deformity	86/332 (25.9)	126/632 (19.9)	0.034†	19/55 (34.5)	60/249 (24.1)	0.174
Dactylitis (ever)	132/443 (29.8)	281/948 (29.6)	0.953	19/74 (25.7)	105/334 (31.4)	0.330
Enthesitis (ever)	118/418 (28.2)	156/883 (17.7)	<0.001†	17/71 (23.9)	83/311 (26.7)	0.617
Nail involvement	225/443 (50.7)	281/948 (29.6)	0.032†	38/74 (51.4)	174/334 (52.1)	0.908
MDA	39/101 (38.6)	106/214 (49.5)	0.045†	8/17 (47.1)	28/77 (36.4)	0.412
BASFI, mean ± SD	2.9 ± 2.4	3.1 ± 2.4	0.626	2.9 ± 2.3	2.9 ± 2.3	0.952
BASDAI, mean ± SD	4.2 ± 2.4	3.9 ± 2.5	0.191	4.3 ± 2.2	4.1 ± 2.1	0.598
HAQ, mean ± SD	0.76 ± 0.7	0.71 ± 0.6	0.538	0.88 ± 0.7	0.72 ± 0.7	0.144
RF positivity	55/443 (12.4)	129/948 (13.6)	0.610	11/74 (14.9)	41/334 (12.3)	0.546

* Values are no./total no. (%) unless indicated otherwise. PsA = psoriatic arthritis; FH = family history; BMI = body mass index; DIP = distal interphalangeal; MDA = minimal disease activity; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; RF = rheumatoid factor.

† Significant.

having PsA in addition to psoriasis in their family and therefore were excluded from further analysis. The onset of psoriasis occurred earlier in patients with a family history of psoriasis compared to those with a family history of PsA (mean ± SD age 28.1 ± 14.4 years versus 31.9 ± 14.8 years; $P < 0.001$) (Table 1).

There were differences in the type of skin lesions according to family history of psoriasis or PsA. Plaque psoriasis was more common in family history of psoriasis, while there was an increased frequency of pustular psoriasis in family history of PsA (Figure 1).

Univariate analysis of the effect of family history on disease characteristics. In comparison to patients with no family history, having a family member with psoriasis was a risk factor for nail disease, enthesitis, plaque psoriasis, and younger age of onset of psoriasis. Also, women had more family history of psoriasis (Table 2).

Similarly, when compared to patients with no family history, having a family member with PsA was a risk factor for the presence of deformities and protective against having plaque

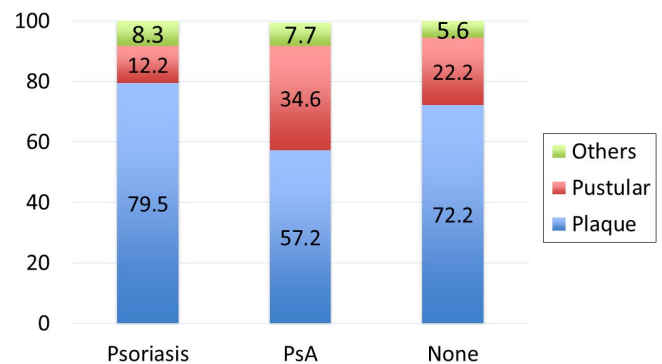


Figure 1. Distribution of skin lesions according to family history. Numbers are given as percentages. PsA = psoriatic arthritis.

Table 2. Univariate and multivariate analysis in patients with family history of psoriasis or PsA*

	Psoriasis vs. none, univariate		Psoriasis vs. none, multivariate†		PsA vs. none, univariate		PsA vs. none, multivariate†		PsA vs. psoriasis, univariate		PsA vs. psoriasis, multivariate‡	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age at psoriasis onset, years	0.985 (0.976–0.994)	0.001¶	0.976 (0.964–0.989)	<0.0001¶	1.002 (0.986–1.019)	0.763	0.995 (0.973–1.018)	0.670	1.018 (1.000–1.036)	0.046¶	1.022 (0.997–1.047)	0.085
Sex	1.317 (1.052–1.786)	0.020¶	1.213 (0.828–1.777)	0.321	1.042 (0.640–1.697)	0.868	0.814 (0.420–1.575)	0.541	1.315 (0.779–2.219)	0.305	0.636 (0.304–1.330)	0.636
Nail involvement (ever)	1.353 (1.054–1.737)	0.018¶	0.989 (0.678–1.442)	0.952	1.313 (0.818–2.109)	0.259	1.329 (0.679–2.602)	0.406	0.971 (0.586–1.606)	0.908	1.252 (0.597–2.627)	0.552
Enthesitis (ever)	1.709 (1.261–2.317)	0.001¶	1.931 (1.276–2.922)	0.002¶	1.467 (0.828–2.599)	0.189	0.832 (0.361–1.917)	0.665	0.858 (0.471–1.563)	0.617	0.421 (0.173–1.025)	0.057
Presence of deformities	0.784 (0.553–1.113)	0.174	1.293 (0.819–2.041)	0.269	1.926 (1.093–3.501)	0.024¶	2.557 (1.250–5.234)	0.010¶	1.535 (0.825–2.854)	0.176	2.143 (1.052–5.367)	0.037¶
Plaque psoriasis	1.461 (1.019–2.096)	0.039¶	1.399 (0.884–2.214)	0.151	0.523 (0.294–0.930)	0.027¶	0.417 (0.213–0.816)	0.011¶	0.358 (0.189–0.675)	0.002¶	0.324 (0.152–0.694)	0.004¶

* PsA = psoriatic arthritis; OR = odds ratio; 95% CI = 95% confidence interval.

† N = 603.

‡ N = 473.

§ N = 212.

¶ Significant.

psoriasis (Table 2). Family history of PsA versus psoriasis was a risk factor for plaque psoriasis. This group also had psoriasis at an older age.

Multivariate analysis of the effect of family history on disease characteristics. In the multivariate analysis, in comparison to patients with no family history, having a family member with psoriasis remained a risk factor for enthesitis and younger age at onset of psoriasis (Table 2). For the comparison of family history of PsA versus none, the same factors that were identified in the univariate analysis remained to be significant in the multivariate analysis. Having a family member with PsA was a risk factor for the presence of deformities and protective against having plaque psoriasis (Table 2). Family history of PsA versus family history of psoriasis had increased risk for deformities and lower risk for plaque psoriasis.

The effect of paternal versus maternal transmission. Because previous studies have demonstrated a difference between paternal versus maternal transmission (6), further analysis was made to test a similar effect in our registry. A total of 174 patients had an affected parent (psoriasis or PsA). A total of 92 of these patients (53%) had an affected father; 82 patients (47%) had an affected mother. There was no difference in disease characteristics among patients whose father or mother was affected (data not shown).

DISCUSSION

The genetic load of psoriasis and PsA has been well described in the literature, as has the effect of family history of psoriasis and/or PsA on disease outcomes (2,3,6,7). However, the differences between psoriasis and PsA in family history have not been examined before. To the best of our knowledge, this is the first study that has shown that having family member(s) with PsA versus psoriasis has an impact on the disease phenotype and severity, with patients who have a family history of PsA having an increased risk of pustular psoriasis and more deformities compared to a family history of psoriasis.

A large number of genetic loci have been described in psoriasis in the last decade by the genome-wide association studies. Fewer studies have been conducted to identify PsA risk variants (7–11). The studies show that the significant differences in the genetic architecture of psoriasis and PsA may also be reflected in the phenotypic characteristics of these diseases. Differences in the strength of association with psoriasis and PsA have been repeatedly observed for the major histocompatibility complex, including a stronger association of HLA-C*06 with psoriasis and a stronger association of HLA-B*27 with PsA. Two other important PsA risk variants resulting from these studies are near *IL23R* and near *TNFAIP3* (10–13). Our data confirm that the genetic differences between psoriasis and PsA in the family may cause a

different phenotype in the index patient. The histologic and clinical differences between plaque and pustular psoriasis may also be due to the genetic differences between patients (14). Innate immune system abnormalities have been shown to be important in pustular psoriasis, with an increased role of interleukin-1 and interleukin-36 in the pathogenesis (15). Paradoxical psoriasis in patients treated with anti-tumor necrosis factor also quite frequently appears to be pustular psoriasis, suggesting a different pathogenic mechanism (16). The simple difference in PsA versus psoriasis in family members may point to a deeper genetic difference in familial cases of psoriatic disease and may be an important factor to consider in the era of personalized medicine.

The literature supports some clinical differences between familial and sporadic cases of PsA, such as an earlier age of onset of psoriasis, more frequent nail involvement, more severe disease, higher frequency of skin lesions prior to arthritis, higher erythrocyte sedimentation rate, and a lower incidence of rheumatoid factor positivity (2,3,6). Similarly, in this cohort we found an earlier age of onset of psoriasis, more frequent nail involvement, more frequent enthesitis, and more frequent deformity in familial cases, which is evidence for the external validity of our cohort and data collection.

Our study has some limitations. Family history is not always easy to obtain because patients may or may not be aware of diseases of their family members, especially for second-degree relatives or if family members have a mild disease. However, this is true for all studies that investigate family history, and the accuracy of this method has been demonstrated previously (17). Family history of psoriasis or PsA was found in 31.9% of the patients in our study, which confirms external validity and is in agreement with the literature (2). Our data are only based on observations, and lack of genetic analysis in the patients prevents us from drawing firm conclusions. Also, the data were collected in 35 centers, and there may be variations on data collection across centers despite the precautions to enhance homogeneity taken prior the study.

In conclusion, family history of psoriasis and PsA has an impact on skin phenotypes, musculoskeletal features, and disease severity. The link between family history of psoriasis/PsA and pustular/plaque phenotypes may point to a different genetic background and pathogenic mechanisms in these subsets.

ACKNOWLEDGMENT

The authors thank all the collaborators for their participation.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version

to be submitted for publication. Dr. Aydin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Solmaz, Bakirci, Kimyon, Gunal, Dogru, Bayindir, Dalkilic, Ozisler, Can, Akar, Cetin, Kilic, Tarhan, Kucuksahin, Omma, Gonullu, Yildiz, Ersozlu, Cinar, Al-Onazi, Erden, Tufan, Yilmaz, Pehlevan, Kalyoncu, Aydin.

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