Scandinavian Journal of Rheumatology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/irhe20

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**To cite this article:** K Juneblad , A Kastbom , L Johansson , S Rantapää-Dahlqvist , P Söderkvist & G-M Alenius (2020): Association between inflammasome-related polymorphisms and psoriatic arthritis, Scandinavian Journal of Rheumatology, DOI: 10.1080/03009742.2020.1834611

**To link to this article:** https://doi.org/10.1080/03009742.2020.1834611



Published online: 10 Dec 2020.

# Association between inflammasome-related polymorphisms and psoriatic arthritis

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**Objective:** Psoriatic arthritis (PsA) is a heterogeneous inflammatory disease associated with psoriasis. Underlying genetic factors are considered important for disease expression and prognosis of PsA. Interleukin-1β-regulating protein complexes called inflammasomes are associated with several inflammatory diseases, e.g. rheumatoid arthritis and psoriasis. The aim was to determine whether inflammasome-related genetic variation is associated with PsA susceptibility or different disease phenotypes.
**Method:** DNA from 724 patients with PsA and 587 population-based controls from northern Sweden was analysed for single-nucleotide polymorphisms in *NLRP3*-Q750K (rs35829419), *NLRP3* (rs10733113), *CARD8*-C10X (rs2043211), *NLRP1* (rs8079034), and *NLRP1* (rs878329).
**Results:** Significant associations were found with the genotype AA (vs AT+TT) of rs2043211 for PsA patients compared with controls [odds ratio (OR), 95% confidence interval (CI) 1.32 (1.05–1.65), p = 0.016]; and between the C-allele of rs878329 and axial involvement of PsA [OR (95% CI) 1.37 (1.02–1.84), p = 0.035], the T-allele of rs8079034 with prescription of conventional synthetic disease-modifying anti-rheumatic drugs [OR (95% CI) 1.76 (1.23–2.53), p = 0.0020], the G-allele of rs10733113 and patients with a skin disease with early onset [OR (95% CI) 1.58 (1.13–2.21), p = 0.007], and the C-allele of rs35829419 and a destructive/deforming disease [OR (95% CI) 1.63 (1.04–2.55), p = 0.030].
**Conclusions:** This study is the first to show an association with a genetic polymorphism in an inflammasome-related gene, *CARD8*-C10X (rs2043211), in patients with PsA. Associations between different phenotypes of PsA and different polymorphisms of the inflammasome genes were also found. Our results indicate the involvement of inflammasome genes in the pathogenesis and disease expression of PsA.

Psoriatic arthritis (PsA) is a heterogeneous inflammatory disease associated with psoriatic skin disease. Not only does it exhibit significant intraindividual variation, with phenotypes ranging from mild monoarthritis/oligoarthritis to severe erosive polyarthritis comparable with rheumatoid arthritis (RA), but in addition, the disease course may fluctuate over time within the same patient. The exact prevalence of PsA is unknown. In two register-based population studies from Denmark and Sweden the prevalence was estimated at 0.2% (1, 2). In contrast to RA, manifestations such as dactylitis and enthesitis are common in PsA, as in patients with other diseases within the seronegative spondylarthropathy group (3, 4). Also in contrast to RA, most individuals with PsA are seronegative for rheumatoid factor and anti-citrullinated protein/peptide antibodies (5, 6).

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Accepted 6 October 2020

Several possible mechanisms have been suggested to be involved in the aetiology, disease expression, and prognosis of PsA, such as different genetic and environmental factors. Other mechanisms have also been of interest; for example, hyaluronan expression seems to be a possible factor in the inflammatory pathology of PsA acting as a biomarker for disease severity, resistance to treatment, and worse outcome (7). The present study focuses on genes related to inflammasomes.

Underlying genetic factors that regulate immunological expression are considered important in psoriasis and PsA. A population study of the Icelandic population showed a 39-fold increased risk of developing PsA if a first degree relative was affected (8), which can be compared with the corresponding risks of developing psoriasis (eight times increased risk) and RA (two to three times increased risk) (9). Thus, indications exist for a strong genetic impact in the development of PsA.

In recent years, the interleukin-1β (IL-1β)-regulating protein complexes called inflammasomes have been shown to have associations with several inflammatory



DOI: 10.1080/03009742.2020.1834611

diseases. Inflammasomes consist of different proteins which, when assembled, activate pro-caspase-1 and subsequent cleavage of pro-IL-1β to active IL-1β.

In research on families with psoriasis, polymorphisms for different genotypes in patients with more widespread psoriasis [*NLRP3* (rs10733113G)], as well as in patients with psoriasis compared with healthy controls [*CARD8*-C10X (rs2043211)], were found (10). Two other single-nucleotide polymorphisms (SNPs) in the *NLRP1* gene (rs8079034C and rs878329C) have shown increased transmission to affected family members in families with psoriasis, and homozygosity for rs837329C correlated with a younger age of onset of psoriasis (11).

Moreover, associations between *CARD8* and *NLRP3* SNPs and other autoinflammatory diseases such as ankylosing spondylitis (AS) and Crohn's disease have been reported (12, 13). Studies on RA have proposed a possible impact on disease expression and susceptibility, but the results are conflicting (14–16).

So far, only one study has been published in which SNPs in the inflammasome genes have been investigated in PsA patients (17). In that study, no associations were found with PsA patients in comparison with population controls. However, this study was not performed in a Swedish population, and inflammasome-related genetic variants have been shown to play important roles in other inflammatory diseases (18, 19). Therefore, we selected five SNPs related to the NLRP1 and NLRP3 inflammasomes with previously described associations with inflammatory diseases (10–15).

## Method

In this study, 724 patients (337 males and 387 females) with PsA and 587 population controls (153 males and 434 females) from the Medical Biobank of northern Sweden were included. The patients were enrolled during 1995–2017 at the Department of Rheumatology Västerbotten, University Hospital, Umeå (n = 571), Department of Rheumatology Örnsköldsvik Hospital, Örnsöldsvik (n = 55), and Department of Rheumatology Östersund Hospital, Östersund (n = 98). Inclusion criteria were age > 18 years and a clinical PsA diagnosis settled by a rheumatologist. All patients gave their written, informed consent. The majority of patients were examined according to a study protocol (Juneblad and Alenius) and all patients' records and available radiographs were carefully read (Juneblad and Alenius) to validate the diagnosis and classify the disease according to the duration of joint and skin disease, smoking habits, and medical treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (cyclosporine, hydroxychlorokine, leflunomide, methotrexate, sodium aurothiomalate, or sulfasalazine) or biological disease-modifying anti-rheumatic drugs (bDMARDs) (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, or ustekinumab). Destructive/deforming disease was defined as either typical radiological changes (e.g. erosions, juxta-articular new bone formation) and/or irreversible deformations (e.g. ankylosis, subluxations, and/or loss of function or reduced mobility) on clinical examination. Measurable inflammation was defined as erythrocyte sedimentation rate ≥ 20 mm/h and/or C-reactive protein ≥ 10 mg/L in combination with clinically active PsA disease. In some cases, complementary information was collected from patient questionnaires owing to a lack of information in the patient's medical record. Demographic data for the patients during the time of the investigation and/or at the time of reading the patients' medical records are presented in Table 1.

Blood samples were collected and stored at −80°C. DNA was extracted from ethylenediaminetetraacetic acid (EDTA)-treated whole blood using the salting out method, for patients included before 2011 (n = 445), and for the remaining patients and controls with the FlexiGene DNA kit (250) (QIAGEN, Hilden, Germany). The selection of SNPs was based on their previously reported associations with related diseases. A total of five SNPs was analysed: two in *NLRP3* [rs35829419 (Q705K), rs10733113], one in *CARD8* [rs2043211 (C10X)], and two in *NLRP1* [rs8079034, rs878329]. Genotypes for the selected SNPs were determined by the TaqMan® SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. The samples were analysed on a 7900 HT Fast Real-Time PCR System (Applied Biosystems).

### Statistics

All SNPs, in both patients and controls, were in Hardy–Weinberg equilibrium. The chi-squared-test was used for testing categorical data between groups. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs). All p values refer to two-sided tests, with $p \leq 0.05$ considered statistically significant. All statistical calculations were performed using SPSS 24.0 (IBM Corp., Armonk, NY, USA).

## Results

### Inflammasome polymorphism in PsA in comparison with controls

A significant association was found with the genotype AA (vs AT+TT) of *CARD8*-C10X (rs2043211) for PsA patients compared with controls [$\chi^2 = 5.77$, OR (95% CI) 1.32 (1.05–1.65), p = 0.016]. The allele frequencies (A/T) were also different between patients and controls [A allele: $\chi^2 = 5.31$, OR (95% CI) 0.83 (0.70–0.97), p = 0.021] (Table 2). No associations were found between the other analysed SNPs and PsA in comparison with controls (Table 2).

When patients were grouped according to disease phenotype, the association with genotype AA (vs AT+TT) of *CARD8*-C10X (rs2043211) was slightly increased for patients with peripheral disease [$\chi^2 = 6.6$, OR (95% CI) 1.36 (1.08–1.72), p = 0.010] (Table 3). In the patient

Table 1. Demographic data of patients with psoriatic arthritis (PsA) at the time of investigation of patients' medical records.

| | |
|---|---|
| Age (years) | 59.4 ± 12.4 |
| Age at first PsA symptoms (years) | 41.6 ± 14.8 |
| Age at diagnosis of skin disease (years) | 31.5 ± 16.3 |
| Male gender | 337 (46.5) |
| Smoking (ever) | 357 (54) |
| Smoking (current) | 96 (14.5) |
| Skin psoriasis type 1 (onset < 40 years) | 440 (67.3) |
| Fulfilling CASPAR | 633 (91.3) |
| Fulfilling Moll and Wright criteria | 690 (95.8) |
| DIP joint disease | 2 (0.3) |
| Predominantly axial disease | 35 (4.9) |
| Monoarthritis/oligoarthritis | 354 (49.2) |
| Polyarthritis | 291 (40.4) |
| Arthritis mutilans | 8 (1.1) |
| Disease phenotype | |
| Peripheral disease only | 600 (82.9) |
| Monoarthritis/oligoarthritis | 328 (45.3) |
| Polyarthritis | 270 (37.3) |
| Axial disease without peripheral arthritis | 25 (3.5) |
| Axial and peripheral disease | 77 (10.7) |
| Spondyloarthritis | 20 (2.8) |
| Nail psoriasis | 247 (42.6) |
| Psoriasis of the skin | 673 (97.3) |
| Psoriasis vulgaris | 648 (93.4) |
| Guttate psoriasis | 4 (0.6) |
| Pustulosis palmoplantaris only | 21 (3) |
| Inverse psoriasis | 2 (0.3) |
| Destructive/deforming disease, X-ray and/or clinical | 315 (46.4) |
| Measurable inflammation when clinically active disease | 259 (47.2) |
| bDMARD ever | 103 (14.5) |
| csDMARD ever | 504 (70) |

Data are shown as mean ± sd or n (%).
CASPAR, ClASsification criteria for Psoriatic ARthritis; DIP, distal interphalangeal; bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug.

group with axial disease, (regardless of peripheral involvement), no such association was found [$\chi^2$ = 0.54, OR (95% CI) 1.17 (0.76–1.80), p = 0.46]. Upon further subcategorization into monoarthritis/oligoarthritis and polyarthritis, the significant difference from controls remained for the group with polyarthritis [$\chi^2$ = 6.14, OR (95% CI) 1.45 (1.07–1.96) p = 0.013], but not for the group with monoarthritic/oligoarthritic disease phenotype [$\chi^2$ = 3.22, OR (95% CI) 1.29 (0.98–1.70) p = 0.073] (Table 3).

### Disease phenotypes in relation to other genotypes

Among PsA patients, a significant association was seen with the C-allele of *NLRP1* rs878329 and patients with axial involvement of disease [$\chi^2$ = 4.45, OR (95% CI) 1.37 (1.02–1.84), p = 0.035] (Table 4). When different genotypes were compared, a significantly higher frequency of the genotype CC (vs GC+GG) was detected in the subgroup with axial involvement of the disease [$\chi^2$ = 5.82, OR (95% CI) 1.84 (1.11–1.84), p = 0.016] (Table 4). The *NLRP3* rs10733113 G-allele was associated with patients with a skin disease of early onset (psoriasis type 1, onset < 40 years) [$\chi^2$ = 7.38, OR (95% CI) 1.58 (1.13–2.21), p = 0.007] (Table 4). In the subgroup of PsA with destructive/deforming disease, a significant association was found with the C-allele of *NLRP3*-Q705K (rs35829419) [$\chi^2$ = 4.72, OR (95% CI) 1.63 (1.04–2.55), p = 0.030] and destructive disease (Table 4). In addition, *NLRP1* rs8079034T was significantly associated with PsA patients who were ever prescribed a csDMARD compared with those never treated with csDMARDs [$\chi^2$ = 9.59, OR (95% CI) 1.76 (1.23–2.53), p = 0.0020] (data not shown).

No other significant differences in genotype distribution or allele frequencies were detected for gender, nail psoriasis, measurable inflammation with clinically active PsA disease, or bDMARDs (data not shown).

## Discussion

In this study, an association between the genotype AA of *CARD8*-C10X (rs2043211) and PsA was found. This polymorphism of *CARD8*-C10X is a functional mutation, with the minor allele (T) causing a nonsense mutation leading to a truncated CARD8 protein. The results are in agreement with a study on patients with AS (12). Also, in a study on psoriasis, the allele frequencies for the *CARD8*-

Table 2. Frequencies of genotypes and alleles of *NLRP1* (rs878329, 8079034), *NLRP3* (rs10733113, 35829419), and *CARD8*-C10X (rs2043211) in patients with psoriatic arthritis (PsA) and controls.

| | Controls | PsA | OR (95% CI) | $\chi^2$ | p |
|---|---|---|---|---|---|
| *NLRP1* (rs878329)† | | | | | |
| CC | 97 (17) | 122 (17) | Ref. | | |
| GC | 273 (48) | 358 (50) | 1.04 (0.77–1.42) | 0.070 | 0.79 |
| GG | 206 (36) | 236 (33) | 0.91 (0.66–1.26) | 0.32 | 0.57 |
| GG (vs GC+CC) | 206 (36) | 236 (33) | 0.88 (0.70–1.11) | 1.11 | 0.29 |
| C allele | 476(41) | 602(42) | 1.04 (0.89–1.22) | 0.29 | 0.59 |
| *NLRP1* (rs8079034)‡ | | | | | |
| TT | 28 (4.9) | 24 (3.3) | Ref. | | |
| CT | 172 (30) | 207 (29) | 1.40 (0.78–2.53) | 1.32 | 0.25 |
| CC | 377 (65) | 487 (68) | 1.51 (0.86–2.64) | 2.07 | 0.15 |
| CC (vs CT+TT) | 377 (65) | 487 (68) | 0.89 (0.71–1.13) | 0.89 | 0.35 |
| T allele | (19.8) | (17.8) | 0.88 (0.72–1.07) | 1.69 | 0.19 |
| *NLRP3* (rs10733113)§ | | | | | |
| AA | 15 (2.6) | 13 (1.8) | Ref. | | |
| GA | 142 (25) | 156 (22) | 1.27 (0.58–2.81) | 0.36 | 0.55 |
| GG | 421 (73) | 548 (76) | 1.50 (0.70–3.25) | 1.13 | 0.29 |
| GG (vs GA+AA) | 421 (72.8) | 548 (76.4) | 1.21 (0.94–1.56) | 2.19 | 0.14 |
| A allele | 172 (15) | 182 (13) | 0.83 (0.67–1.04) | 2.60 | 0.11 |
| *NLRP3*-Q705K (rs35829419)‖ | | | | | |
| AA | 3 (0.5) | 2 (0.3) | Ref. | | |
| CA | 78 (13.3) | 94 (13.1) | 1.81 (0.29–11.1) | 0.42 | 0.52 |
| CC | 505 (86.2) | 622 (86.6) | 1.85 (0.31–11.10) | 0.46 | 0.50 |
| CC (vs CA+AA) | 505 (86.2) | 622 (86.6) | 1.04 (0.76–1.43 | 0.06 | 0.813 |
| A allele | (6.7) | (6.8) | 0.95 (0.70–1.29) | 0.104 | 0.747 |
| *CARD8*-C10X (rs2043211)¶ | | | | | |
| TT | 77 (14) | 82 (11) | Ref. | | |
| AT | 274 (48) | 312 (44) | 1.07 (0.75–1.52) | 0.14 | 0.71 |
| AA | 218 (38) | 322 (45) | 1.39 (0.97–1.98) | 3.27 | 0.071 |
| AA (vs AT+TT) | 218 (38) | 322 (45) | 1.32 (1.05–1.65) | 5.77 | 0.016* |
| T allele | 428 (38) | 476 (33) | 0.83 (0.70–0.97) | 5.31 | 0.021* |

Data are shown as n (%).
†Controls n = 576, PsA n = 716.
‡Controls n = 577, PsA n = 718.
§Controls n = 578, PsA n = 717.
‖Controls n = 586, PsA n = 718.
¶Controls n = 569, PsA n = 716.
OR, odds ratio; CI, confidence interval.
*Significant difference ($p \leq 0.05$).

C10X (rs2043211) were significantly different between cases and controls when analysed using logistic regression analysis (10). In early RA, *CARD8*-C10X has been associated with inflammatory activity (20). In this study, no associations were found between rs2043211 and any of the examined PsA disease phenotypes, including destructive/deforming disease and a disease phenotype with measurable inflammation in active disease.

When patients with or without axial involvement of disease were investigated, a significant association with the C-allele of *NLRP1* rs878329 was discovered. In a family study on psoriasis, an increased transmission of rs878329C to affected family members was found and homozygosity was related to a younger age of disease onset (11). However, when we separated the PsA patients according to psoriasis with and without an early onset (< 40 years) (psoriasis type 1), no association with *NLRP1* rs878329 was detected. Instead, we found an association with psoriasis type 1 and the G allele of the *NLRP3* rs10733113 SNP. The G-allele was also found to be significantly transmitted to individuals with more widespread psoriasis in a family-based study (10). Since psoriasis type 1 is generally considered to be associated with a more severe psoriasis, our results strengthen the putative role of this polymorphism for the severity of psoriasis skin disease.

An association was found between the *NLRP1* rs8079034T allele and patients prescribed a csDMARD. Prescription of DMARDs can be considered a surrogate marker for a severe disease, and thus the association could implicate a more severe disease in our patients. *NLRP1* rs8079034 has also previously been investigated in psoriasis (11) and the *NLRP1* rs8079034C allele was transmitted to a higher extent to affected family members. As in our study, no significant difference between patients and controls was detected for this polymorphism.

Table 3. Comparison of genotype frequencies of *CARD8*-C10X (rs2043211) in patients with psoriatic arthritis (PsA) stratified for different disease expression and controls.

| *CARD8*-C10X (rs2043211) | Controls n (%) | PsA patients n (%) | OR (95% CI) | $\chi^2$ | p |
|---|---|---|---|---|---|
| | Controls (n = 716) | Peripheral disease (n = 592) | | | |
| TT | 77 (14) | 66 (11) | Ref. | | |
| AT | 274 (48) | 255 (43) | 1.09 (0.75–1.57) | 0.19 | 0.66 |
| AA | 218 (38) | 271 (46) | 1.45 (1.00–2.11) | 3.82 | 0.051 |
| AA (vs AT+TT) | 218 (38) | 271 (46) | 1.36 (1.08–1.72) | 6.63 | 0.010* |
| | Controls (n = 716) | Axial disease (n = 25) | | | |
| TT | 77 (14) | 11 (44) | Ref. | | |
| AT | 274 (48) | 12 (48) | 1.69 (0.37–7.69) | 0.46 | 0.49 |
| AA | 218 (38) | 2 (8) | 1.94 0.42–8.96) | 0.75 | 0.39 |
| AA(vs AT+TT) | 218 (38) | 2 (8) | 1.26 (0.56–2.84) | 0.33 | 0.57 |
| | Controls (n = 716) | Axial and peripheral disease (n = 77) | | | |
| TT | 77 (14) | 10 (13) | Ref. | | |
| AT | 274 (48) | 35 (45) | 0.98 (0.47–2.08) | 0.002 | 0.96 |
| AA | 218 (38) | 32 (42) | 1.13 (0.53–2.41) | 0.10 | 0.75 |
| AA (vs AT+TT) | 218 (38) | 32 (42) | 1.14 (0.71–1.86 | 0.30 | 0.58 |
| | Controls (n = 716) | Axial with or without peripheral disease (n = 102) | | | |
| TT | 77 (14) | 12 (12) | Ref. | | |
| AT | 274 (48) | 47 (46) | 1.10 (0.55–2.18) | 0.076 | 0.78 |
| AA | 218 (38) | 43 (42) | 1.26 (0.64–2.16) | 0.45 | 0.50 |
| AA (vs AT+TT) | 218 (38) | 43 (42) | 1.17 (0.76–1.80) | 0.54 | 0.46 |
| | Controls (n = 716) | Peripheral disease and polyarthritic phenotype (n=266) | | | |
| TT | 77 (14) | 30 (11) | Ref. | | |
| AT | 274 (48) | 110 (41) | 1.03 (0.64–1.66) | 0.015 | 0.90 |
| AA | 218 (38) | 126 (47) | 1.48 (0.92–2.39) | 2.66 | 0.10 |
| AA (vs TA+TT) | 218 (38) | 126 (47) | 1.45 (1.07–1.96) | 6.14 | 0.013* |
| | Controls (n = 716) | Peripheral disease and monoarthritic/oligoarthritic phenotype (n = 324) | | | |
| TT | 77 (14) | 36 (11) | Ref. | | |
| AT | 274 (48) | 144 (44) | 1.12 (0.72–1.75) | 3.22 | 0.073 |
| AA | 218 (38) | 144 (44) | 1.41 (0.90–2.21) | 2.30 | 0.13 |
| AA (vs TA+TT) | 218 (38) | 144 (44) | 1.29 (0.98–1.70) | 3.22 | 0.073 |

Data are shown as n (%).
OR, odds ratio; CI, confidence interval.
*Significant difference ($p \leq 0.05$).

In PsA patients, we found a significant association between the *NLRP3*-Q705K rs35829419 SNP and destructive/deforming disease, with a smaller proportion with this disease phenotype being carriers of the variant allele, indicating a role in PsA disease severity.

To our knowledge, only one previous study has been published where SNPs in the inflammasome genes have been studied in patients with PsA (17). In that study, both rs2043211 in *CARD8* and rs878329 in *NLRP1* were analysed in comparison with population controls, although no significant associations were detected. There are several possible reasons underlying the differing results in our study compared to the previous Danish study. First, we studied different populations, with differences in background genetics, lifestyle exposures, and healthcare systems. Secondly, the previous study had a slightly smaller patient sample size (n = 459), and recruited PsA patients from the DANBIO registry, meaning that all patients were treated with at least csDMARDs, and many of them also bDMARDs. Our population was not selection biased for treatment, but instead represents a cross-sectional sample of PsA patients where 70% had ever been treated with csDMARDs.

In our study, an association between the *CARD8*-C10X polymorphism and PsA was found, thus showing an association between a polymorphism in an inflammasome gene and PsA, indicating a possible involvement in the pathogenesis of the PsA disease. This gene has not previously been found to be associated with PsA in genome-wide association studies (GWAS). This, however, does not rule out a possible association, particularly an association with a subpopulation or a subgroup of patients. GWAS also have limitations, e.g. a very high level of significance is needed for an association to be detected in complex diseases such as PsA, while SNPs with modest effects can be missed (21). In addition, our study is, to the best of our knowledge, the first to investigate possible associations between genes related to the inflammasome

Table 4. Distributions of frequencies of genotypes and alleles of *NLRP1* (rs878329) and *NLRP3* (rs35829419 and rs10733113) in different phenotypes of psoriatic arthritis.

| | Axial disease | Peripheral disease | OR (95% CI) | $\chi^2$ | p |
|---|---|---|---|---|---|
| NLRP1 rs878329 | N = 107 | N = 539 | | | |
| CC | 26 (24) | 80 (15) | Ref. | | |
| GC | 51 (48) | 275 (51) | 0.57 (0.33–0.97) | 4.31 | 0.038* |
| GG | 30 (28) | 184 (34) | 0.50 (0.28–0.90) | 5.41 | 0.020* |
| CC (vs GC+GG) | 26 (24) | 80 (15) | 0.54 (0.33–0.90) | 5.82 | 0.016* |
| C carriage | 77 (72) | 355 (66) | 1.33 (0.84–2.10) | 1.50 | 0.22 |
| C allele | 103 (48) | 435(41) | 1.37 (1.02–1.84) | 4.45 | 0.035* |
| | Psoriasis type 1† | Not psoriasis type 1 | | | |
| NLRP3 rs10733113 | N = 439 | N = 210 | | | |
| AA | 5 (1) | 8 (4) | Ref. | | |
| GA | 87 (20) | 53 (25) | 2.63 (0.82–8.45) | 2.78 | 0.095 |
| GG | 347 (79) | 149 (71) | 3.73 (1.20–11.58) | 5.89 | 0.015* |
| GG (vs GA+AA) | 347 (79) | 149 (71) | 1.54 (1.06–2.25) | 5.16 | 0.023* |
| G carriage | 434 (99) | 202 (96) | 3.44 (1.11–10.64) | 5.16 | 0.023* |
| G allele | 781(89) | 351(84) | 1.58 (1.13–2.21) | 7.38 | 0.007* |
| | Destructive disease | Non-destructive disease | | | |
| NLRP3 Q705K rs35829419 | N = 314 | N = 360 | | | |
| AA | 0 (0) | 2 (0.3) | – | | |
| CA | 32 (10) | 54 (15) | Ref. | | |
| CC | 282 (90) | 304 (84) | 1.56 (0.98–2.50) | 3.59 | 0.058 |
| CC (vs CA+AA) | 282 (90) | 304 (84) | 1.62 (1.02–2.58 | 4.25 | 0.039* |
| C allele | 596 (95) | 662 (92) | 1.63 (1.04–2.55) | 4.72 | 0.030* |

Data are shown as n (%). Only single-nucleotide polymorphisms and phenotypes with significant associations are shown.
†Skin psoriasis with onset before 40 years.
OR, odds ratio; CI, confidence interval.
*Significant difference ($p \leq 0.05$).

and different phenotypes of PsA. Novel differences between the various PsA disease phenotypes were identified, which could inspire further studies in this area.

Strengths of our study include the relatively large number of very well-characterized patients with PsA. Also, patients and controls were selected from the same geographical area of northern Sweden, which is important in genetic studies to avoid allelic differences due to differences in populations. Patients with skin psoriasis only were not examined in this study, which could be considered as a limitation. The study was designed as an initial investigation to examine inflammasomes in PsA patients and a population-based control group was therefore selected. The next step is to study patients with psoriasis in comparison with PsA patients and a control population within the same geographical area.

No correction for multiple testing was performed. This was an active choice to avoid the risk of missing a true association (type 2 error) while trying to avoid accepting a false association (type 1 error). Future studies are needed to further investigate our findings.

## Conclusion

This study is the first to show an association with a genetic polymorphism in an inflammasome-related gene, *CARD8*-C10X (rs2043211), in patients with PsA. Associations between different phenotypes of PsA and different polymorphisms of the inflammasome genes were also found. Our results indicate the involvement of inflammasome genes in the pathogenesis and disease expression of PsA.

## Acknowledgements

The authors thank Viktoria von Zweigbergk for technical assistance.

The work was funded with grants from "Psoriasisförbundet" (The Swedish organization against Psoriasis) and Västerbotten County Council, Sweden.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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