IDENTIFICATION OF VARIANTS IN GENES ASSOCIATED WITH AUTOINFLAMMATORY DISORDERS IN A COHORT OF PATIENTS WITH PSORIATIC ARTHRITIS

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ABSTRACT

Objectives Besides adaptive immunity genes, genetic risk factors for psoriatic arthritis (PsA) include innate immunity loci, which suggest an autoinflammatory disease mechanism, at least in a subset of patients. Here, we aimed at investigating the autoinflammatory genetic background of PsA.

Methods A total of 120 patients with PsA visiting the outpatient clinics of the Hannover University hospital underwent targeted next-generation sequencing, searching for variations in genes linked with inborn errors of immunity classified as autoinflammatory disorders (AIDs). Deleteriousness of rare variants was evaluated through in silico analysis.

Results We found 45 rare predicted deleterious variants in 37 out of 120 (30.8%) patients with PsA. Relatively common were variants in AP1S3, PLCB2, NOD2 and NLRP12. All 45 variants were monoallelic and 25 of them, identified in 20 out of 120 (16.7%) patients, were localised in genes associated with autosomal dominant (AD) disorders. Detection of those variants is associated with pustular psoriasis or a coexisting inflammatory bowel disease (IBD).

Conclusions Approximately 30% of patients with PsA harboured at least one variant in a gene associated with an AID, suggesting an autoinflammatory disease mechanism. Detection of variants in genes linked to AD-AIDs may explain extra-articular manifestations of PsA, such as pustular psoriasis and IBD.

INTRODUCTION

Psoriatic arthritis (PsA) is a complex inflammatory disease of the joints associated with psoriasis.1 Beyond skin and varying articular features, inflammation in PsA can affect the entheses, the nails, the eyes and the gut.2 The fact that a family history of psoriasis represents a risk factor for the development of PsA, which has been integrated in the 2006 Classification for Psoriatic Arthritis (CASPAR) criteria,3 suggests the importance of genetic factors in the pathogenesis of PsA and its clinical spectrum.4 Genetic risk factors for PsA partially overlap with the ones of psoriasis.5 However, the heritability of PsA appears considerably higher than that of psoriasis, exceeding 80%, according to population-based studies that revealed a 30-fold to 49-fold relative risk in a case of a sibling with PsA.1 5 6 The latter suggests that within the clinical spectrum of psoriatic disease, genetic factors have a stronger influence on the development of arthritis as compared with a skin-only disease.7

Associations with human leucocyte antigen (HLA) class I alleles highlight the role of
adaptive immunity, suggesting an autoimmune pathogenesis for PsA.8–11 The HLA-C*06 has been identified as the main genetic determinant conferring susceptibility to psoriasis.11 Despite its coassociation with PsA, the association with psoriasis is more robust and HLA-C*06 associates with a longer interval between the onset of skin disease and subsequent development of arthritis, which may suggest a rather protective effect on articular involvement.8–10 In contrast, within the HLA-B locus, HLA-B*27 and HLA-B*39 associate with a higher risk for developing PsA as well as with a shorter interval between the onset of psoriasis and the development of arthritis.11–13 Consistent with an autoimmune inflammation in PsA is the recently reported clonal expansion of CD8+ T cells in the synovial fluid of PsA.11 Further, diverse autoantibodies have been reported in PsA, although their pathogenicity has not been established.12,13 In addition to HLA, non-HLA innate immunity genes have been associated with psoriasis and PsA, suggesting the pathogenic relevance of innate immune dysfunction.1,14 Variants in genes involved in NF-κB activity, such as in TNFAIP3, encoding the protein A20, NFKBIA, encoding 1κBα, which both negatively regulates NF-κB, as well as variants in CARD14, encoding the caspase recruitment domain-containing protein 14 (CARD14), which is involved in the initiation of the NF-κB signalling pathway, have been identified through genome-wide association studies (GWAS) to confer susceptibility for both psoriasis and psoriatic arthritis.14–16

Autoinflammatory diseases are an expanding group of heterogeneous conditions, characterised by inflammation, originating from a dysfunction of the innate immune system.17 The term ‘autoinflammatory’ was initially introduced to describe systemic inflammatory disorders that differ from autoimmune diseases in that high-titre autoantibodies and autoreactive T cells were absent.16 However, according to the current perception, detection of autoantibodies or T cell activation can be part of an autoinflammatory disorder, as long as the activation of the adaptive immune system is not driven from misrecognition of a self-antigen.19 So far, 56 monogenic inborn errors of immunity (IEI) resulting in autoinflammatory disorders are known.20 Their clinical spectrum comprises recurrent fever, mucocutaneous, neurological, gastrointestinal manifestations and rheumatic manifestations. Autoinflammatory pathomechanisms are increasingly recognised in common disorders, including atherosclerosis, gout and Alzheimer’s disease.21–23 and autoinflammation has been suggested to be involved in the pathogenesis of systemic rheumatic diseases, including spondyloarthritis and systemic lupus erythematosus (SLE).24,25

Previous genetic studies have suggested the autoinflammatory aetiology of PsA.14,15 Further, phenotypic traits of monogenic autoinflammatory disorders include features of the psoriatic spectrum, such as psoriasis, arthritis, uveitis and inflammatory bowel disease (IBD).19 Hence, we employed targeted next-generation sequencing (NGS), searching for variants in genes associated with monogenic autoinflammatory disorders in a cohort of patients with PsA, including subgroups of patients with variable articular and extra-articular manifestations.

**PATIENTS AND METHODS**

**Study cohort**

All patients visiting our rheumatology outpatient clinic between October 2020 and March 2021 were screened for the diagnosis of PsA. Diagnosis of PsA has been made according to the 2006 classification criteria for PsA of the CASPAR study group.3 Out of 3646 screened patients, 130 were diagnosed with PsA. A total of 120 of them with available consent and gDNA probe were enrolled in the study. Demographics, clinical and laboratory data were obtained from patients’ medical files. Those included all articular and extra-articular manifestations of the psoriatic spectrum, the age at onset of first psoriatic manifestation and patients actual and previous treatment.

**Targeted NGS**

Targeted NGS has been performed as described previously.20 Briefly, we generated a customised panel of genes associated with IEI grouped as diseases of immune dysregulation or autoinflammatory disorders (online supplemental table 1) with the help of Agilent’s web-based SureDesign application. Blood samples were collected in the immunology outpatient clinics of the Department of Rheumatology and Immunology of Hannover University Hospital. Genomic DNA was extracted by QIAamp DNA Blood Midi Kit (Qiagen) and quantified by Qubit dsDNA BR Assay Kit (ThermoFisher). DNA target enrichment was performed using SureSelect XTHS2 Target Enrichment System for Illumina Sequencing following the manufacturer’s instructions (Agilent’s user manual). Sequencing was performed on an Illumina MiSeq system using an Illumina v2 reagent kit following the manufacturer’s protocol. Data analysis was performed with the help of Agilent’s SureCall software.

**Variant filtering**

The FastQ files were aligned to the human reference genome (UCSC hg19, GRch37) and analysed using Agilent Technologies—SureCall software. Variants were selected according to criteria at the variant level: allele frequency (AF), variant annotation and potential functional effect. Using databases of variants (eg, dbSNP, 1000 Genomes Project, Exome Aggregation Consortium (ExAC), Genome Aggregation Database (gnomAD)) and disease-causing variants (HGMD, OMIM), we selected all private or rare variants with an AF <1%. Furthermore, we kept nonsense variants, variants affecting splice site, frameshift, in-frame indels, start or stop codon changes, as well as missense variants that were predicted deleterious by having a Combined Annotation-Dependent Depletion (CADD) score >15 and a Mutation Significance Cut-off (MSC) score below the CADD score.27–29 Pathogenicity of variants that fulfilled all aforementioned
Psoriatic arthritis

| Table 1 Characteristics of the patients with PsA |
|-----------------------------------------------|
| n=120                                         |
| Age (years) — median (IQR)                    | 50.5 (35–62) |
| Sex, female—n (%)                             | 84 (70)      |
| North European ethnicity—n (%)                | 111 (92.5)   |
| Age at first diagnosis of psoriasis/psoriasis arthritis — median (IQR) | 33.5 (21–43) |
| Psoriasis—n (%)                               | 96 (80)      |
| Pustular psoriasis—n (%)                      | 13 (10)      |
| Nail psoriasis—n (%)                          | 9 (7.5)      |
| Axial SpA—n (%)                               | 35 (29.2)    |
| Enthesiopathy—n (%)                           | 35 (29.2)    |
| Dactylitis—n (%)                              | 11 (9.5)     |
| Anterior uveitis—n (%)                        | 6 (5)        |
| IBD—n (%)                                     | 5 (4.2)      |
| Treatment                                      |              |
| NSAID monotherapy—n (%)                       | 12 (10)      |
| csDMARD—n (%)                                 | 59 (49.2)    |
| TNFi—n (%)                                    | 27 (22.5)    |
| IL-17i—n (%)                                  | 19 (15.8)    |
| IL-23i*—n (%)                                 | 6 (5)        |
| JAKi—n (%)                                    | 10 (8.3)     |
| Other†—n (%)                                  | 5 (4.2)      |

*Including treatment with ustekinumab, targeting both IL-23 and IL-12.
†Including apremilast or bDMARDs not listed above.

Statistical analysis

For statistical calculation, we used GraphPad Prism V.5.00 (GraphPad, La Jolla, California, USA). Descriptive statistics are reported as median and IQR in case of continuous variables and as counts and percentages for dichotomous variables. Categorical variables were compared by the \( \chi^2 \) test. Non-categorical variables were compared with the Mann-Whitney test. All comparisons were two-tailed and \( p<0.05 \) was considered significant.

RESULTS

Characteristics of patients with PsA

The characteristics of all 120 enrolled in the study, including PsA-associated manifestations and treatment, are summarised in table 1. The majority of studied patients had active psoriasis (96/120, 80%) at the time of sample collection. Plaque psoriasis was the most common type of psoriasis, diagnosed in 83 out of 120 (69.2%), followed by pustular psoriasis (13/96, 13.5%). A total of 9 out of 120 (9.4%) had nail psoriasis, which in all cases accompanied skin psoriasis, and mostly plaque psoriasis (8/9). Nearly all patients without psoriasis (i.e., 23/120, 19.2%) had a family history of psoriasis. Overall, 38 out of 120 (31.7) patients had a family history of psoriasis and the majority of them, that is, 34 out of 38 (89.5%) had at least an affected first-degree relative. To our knowledge, all enrolled patients with PsA were unrelated. In addition, we documented all non-psoriatic manifestations of immune dysregulation, and identified 11 out of 120 (9.2%) patients with hypothyroidism, most commonly as a consequence of Hashimoto’s thyroiditis (8/11), 8 out of 120 (6.7%) patients with a history of atopic disease, including atopic dermatitis (6/8) and asthma (4/8), 3 out of 120 (2.5%) patients with giant cell arteritis, 3 out of 120 (2.5%) patients with a history of erythema nodosum, 2 patients with a history of Raynaud’s phenomenon, 2 patients with vitiligo, 2 with a history of Sicca symptoms and 2 with oral aphthosis.

Detection of variants in genes associated with autoinflammatory disorders in patients with PsA

The employed targeted NGS approach included all genes, which were associated with IEI, classified as autoinflammatory disorders (group VII of the International Union of Immunological Societies (IUIS) classification of IEI) as well as genes associated with disorders from alternative groups, that have also been associated with autoinflammatory manifestations. Considering AF as well as measures of deleteriousness, such the CADD and the MSC score of each identified variant, we ended up with a total of 45 rare and likely deleterious germline variations (table 2), which were identified in 37 out of 120 (30.8%) patients (figure 1). All identified variants were monoallelic. A total of 25 variants in genes linked to an autosomal dominant (AD) disorder were detected in 20 out of 120 (16.7%) patients (figure 1 and figure 2A).

Among those, 5 out of 120 (4.2%) patients were identified with a heterozygous variants in \( API53 \) (figure 1). All those five patients harboured either the c.11T>G (p.Phe4Cys) or the c.97C>T (p.Arg33Trp) (table 2). Both the aforementioned \( API53 \) variants have been previously reported as pathogenic and associated primarily with pustular psoriasis.

Among patients with PsA harbouring an \( API53 \) variant, four out of five had pustular psoriasis, whereas one was diagnosed with plaque psoriasis only (online supplemental table 2). In addition to psoriasis, those patients displayed variable arthritis, classified as a rather symmetrical polyarthritis with involvement of the finger joints in three patients and bilateral sacroiliitis in one of the five patients.

Further, we identified five rare variants in \( PLCG2 \) in four patients. \( PLCG2 \) encodes the phospholipase C\( \gamma \)2 (PLC\( \gamma \)2), a signalling mediator primarily expressed by B cells.
| Patient ID | Age | Sex | Gene | Inheritance of gene-associated disorder | Refseq transcript | Coding change | Protein change | gnomAD allele freq. | RS-ID | CADD score | MSC-CADD score | PolyPhen2 score | PolyPhen2 Pred. | SIFT score | SIFT Pred. |
|------------|-----|-----|------|--------------------------------------|-------------------|---------------|---------------|-------------------|-------|------------|----------------|----------------|----------------|------------|------------|
| 3          | 70  | F   | NOD2 | AD                                   | NC_000016.9       | c.1211C>T     | p.Ser404Leu   | 0.0009499         | rs104895431 | 21.400      | 0.019          | 0.266          | Benign        | 0.020      | D          |
| 4          | 60  | F   | NOD2 | AD                                   | NC_000016.9       | c.2377G>A     | p.Val793Met   | 0.001147          | rs104895444 | 22.000      | 0.019          | 0.134          | Benign        | 0.110      | T          |
| 6          | 67  | F   | NOD2 | AR                                   | NM_024570.3       | c.868G>A      | p.Asp90Asn    | 0.0004186         | rs201190805 | 33.000      | 0.278          | 0.987          | Probably damaging | 0.660      | T          |
| 7          | 44  | F   | TYK2 | AR                                   | NM_003331.4       | c.3028G>A     | p.Gly1010Ser  | NA                | NA              | 35.000      | 26.100        | 0.989          | Probably damaging | 0.000      | D          |
| 11         | 49  | M   | AP1S3 | AD                                  | NC_000002.11      | c.111T>G      | p.Phe4Cys     | 0.007891          | rs116107386 | 34.000      | 25.600        | 0.997          | Probably damaging | 0.000      | D          |
| 12         | 23  | F   | TNFAIP3 | AD                              | NC_000006.11      | c.207C>G      | p.Ile69Met    | 0.00002475        | rs548932103 | 16.550      | 3.313          | 0.265          | Benign        | 0.000      | D          |
| 13         | 62  | F   | AP1S3 | AR                                   | NC_000002.11      | c.111T>G      | p.Phe4Cys     | 0.007891          | rs116107386 | 34.000      | 25.600        | 0.997          | Probably damaging | 0.000      | D          |
| 20         | 52  | F   | SHSBP2 | AR                            | NC_000004.11      | c.724del      | p.His242Thrfs*36 | 0.0001389       | rs742750901 | 25.700      | 23.900        | NA            | NA            | NA         | NA         |
| 21         | 33  | F   | COPA | AR                                   | NM_001098398.1    | c.479G>A      | p.Arg169His   | NA                | NA              | 35.000      | 3.313         | 1.000          | Probably damaging | 0.000      | D          |
| 22         | 20  | F   | TNFRSF1A | AD                         | NM_001065.3      | c.334G>A      | p.Val112Met   | 0.00005172        | rs201753543 | 26.100      | 0.015          | 0.417          | Benign        | 0.110      | T          |
| 23         | 79  | F   | IL1R | AR                                   | NM_001318914.1    | c.170G>T      | p.Cys57Phe    | 0.0002121         | rs201638660 | 29.000      | 23.600        | 0.999          | Probably damaging | 0.200      | T          |
| 24         | 61  | F   | LG4 | AR                                   | NC_000013.10      | c.192_193del  | p.Phe64Leufs*21 | NA               | NA              | 29.400      | 0.001          | NA            | NA            | NA         | NA         |
| 26         | 56  | F   | IFIH1 | AR                        | NM_022168.3      | c.1312T>C    | p.Ser438Pro   | 0.0001456         | rs139714761 | 26.200      | 19.330        | 0.973          | Probably damaging | 0.010      | D          |
| 27         | 52  | F   | PLCG2 | AD                          | NM_002661.3      | c.707C>T      | p.Pro236Leu   | 0.0003168         | rs199760975 | 28.200      | 3.313          | 0.999          | Probably damaging | 0.060      | T          |
|            |     |     | PLCG2 | AD                          | NM_002661.3      | c.82A>T       | p.Met288Leu   | 0.01057           | rs61749044  | 24.000      | 3.313          | 0.813          | Possibly damaging | 0.230      | T          |
|            |     |     | HAVCR2 | AR                     | NM_032782.4      | c.291A>G      | p.Ile97Met    | 0.002885          | rs35960726  | 23.700      | 3.313          | 1.000          | Possibly damaging | 0.250      | T          |
| 31         | 25  | M   | HAVCR2 | AD                         | NM_032782.4      | c.302C>T      | p.Thr101Ile   | 0.006496          | rs147827860 | 24.400      | 3.313          | 0.696          | Possibly damaging | 0.080      | T          |
| 38         | 65  | M   | RNASEH2A | AR                      | NM_006397.2      | c.488C>T      | p.Thr163Met   | 0.00001061        | rs1046057251| 29.400      | 10.530         | 0.997          | Probably damaging | 0.010      | D          |
| 39         | 55  | M   | AP1S3 | AD                          | NM_001039569.1   | c.97C>T       | p.Arg33Trp    | 0.007746          | rs138292988 | 34.000      | 25.600        | 0.997          | Probably damaging | 0.000      | D          |
| 47         | 28  | F   | IFIH1 | AR                        | NM_022168.3      | c.1853G>A     | p.Arg618Gln   | 0.0007437         | rs200017837 | 35.000      | 19.330        | 0.999          | Probably damaging | 0.030      | D          |

Continued
| Patient ID | Age | Sex | Gene  | Inheritance of gene-associated disorder | Refseq transcript | Coding change | Protein change | gnomAD allele freq. | CADD score | MSC-CADD score | Poly-Phen2 score | Poly-Phen2 Pred. | SIFT score | SIFT Pred. |
|------------|-----|-----|-------|----------------------------------------|-------------------|--------------|---------------|------------------|------------|---------------|-----------------|----------------|-------------|-------------|
| 53         | 50  | F   | HAVCR2| AR                                      | NM_032782.4       | c.291A>G     | p.Ile97Met     | 0.002885         | 23.700     | 3.313         | 1.000           | Probably damaging | 0.250       | T           |
| 57         | 29  | F   | NFKB1 | AR                                      | NM_003998         | c.322C>T     | p.His108Tyr   | 0.000006574     | 27.500     | 3.313         | 0.632           | Possibly damaging | 0.010       | D           |
| 58         | 50  | F   | PSMG2 | AR                                      | NC_000018.9       | c.467C>A     | p.Thr158Lys   | 0.000004061     | 34.000     | 5.584         | 0.997           | Probably damaging | 0.120       | T           |
| 61         | 20  | M   | RNASEH2B | AR                                      | NM_001142279.2   | c.338T>G     | p.Leu113Arg   | NA               | 31.000     | 0.278         | 0.972           | Probably damaging | 0.020       | D           |
| 63         | 72  | F   | LPIN2 | AR                                      | NM_014646.2       | c.1510C>T    | p.Leu504Phe   | 0.002562         | 28.400     | 16.710        | 0.629           | Possibly damaging | 0.010       | D           |
| 64         | 61  | F   | COPA  | AD                                      | NC_000001.10     | c.1873A>G    | p.Ile625Val   | 0.000001975     | 23.200     | 3.313         | 0.027           | Benign          | 0.030       | D           |
| 65         | 34  | M   | PLCG2 | AD                                      | NM_002661.3      | c.777C>T     | p.Thr268Met   | 0.0005848        | 24.300     | 3.313         | 0.002           | Benign          | 0.020       | D           |
| 67         | 55  | F   | NLRP12| AD                                      | NM_001277126.1   | c.616C>T     | p.Arg206Cys   | 0.00008377      | 23.700     | 23.600        | 0.970           | Probably damaging | 0.130       | T           |
| 70         | 63  | M   | NLRP12| AD                                      | NM_001277126.1   | c.910C>T     | p.His304Tyr   | 0.004426         | 24.000     | 23.600        | 0.958           | Probably damaging | 0.040       | D           |
| 75         | 46  | M   | TREX1 | AR                                      | NC_000003.11     | c.341G>A     | p.Arg114His   | 0.0003023        | 28.100     | 5.605         | 1.000           | Probably damaging | 0.010       | D           |
| 80         | 50  | M   | CARD14| AD                                      | NC_000017.10     | c.249C>A     | p.Asn83Lys    | 0.000003979     | 26.000     | 0.046         | 0.859           | Possibly damaging | 0.570       | T           |
| 81         | 53  | M   | NLRP12| AD                                      | NM_001277126.1   | c.428G>A     | p.Arg143His   | 0.00001194      | 31.000     | 23.600        | 0.945           | Probably damaging | 0.010       | D           |
| 86         | 36  | F   | AP1S3 | AD                                      | NM_001039569.1   | c.977C>T     | p.Arg33Trp    | 0.007746         | 34.000     | 25.600        | 0.997           | Probably damaging | 0.000       | D           |
| 90         | 44  | F   | ADAR  | AR                                      | NM_001111.4      | c.577C>G     | p.Pro193Ala   | 0.002142         | 23.900     | 0.500         | 0.998           | Probably damaging | 0.000       | D           |
| 91         | 61  | F   | I1LRN | AR                                      | NM_001318914.1   | c.170G>T     | p.Cys57Phe    | 0.000210         | 29.000     | 23.600        | 0.999           | Probably damaging | 0.200       | T           |
| 98         | 39  | F   | PLCG2 | AD                                      | NM_002661.3      | c.1194C>G    | p.Ser398Arg   | 0.000004066      | 23.600     | 3.313         | 0.990           | Benign          | NA          | NA          |
| 115        | 55  | F   | AP1S3 | AD                                      | NM_001039569.1   | c.97C>T      | p.Arg33Trp    | 0.007746         | 34.000     | 25.600        | 0.997           | Probably damaging | 0.000       | D           |

**Table 2 Continued**
NK cells and mast cells. The four patients identified with PLCG2 variants displayed variable late-onset seronegative arthritis, which due to the coexistence of plaque psoriasis (3/4) or the family history of psoriasis in one of them has been classified as PsA (online supplemental table 3). Two of the patients also displayed mild hypogammaglobulinemia associated with a history of recurrent respiratory tract infections in one of them.

In addition, four NOD2 variants were identified in three patients. The NOD2 gene encodes an intracellular innate immune receptor and NOD2 mutations have been associated with chronic inflammatory disorders, that is, early-onset sarcoidosis, the Blau syndrome and Crohn’s disease. Two out of four patients harbouring a NOD2 variant displayed Crohn’s disease (online supplemental table 4). All other detected genetic variants are listed in table 2.

**Features of PsA in patients with variants in genes linked to autosomal dominant AIDs**

All psoriatic and non-psoriatic manifestations of immune dysregulation of the 20 out of 120 patients harbouring at least one variant in a gene associated with an AD-AID are presented in table 3. Among those pustular psoriasis was significantly more common in patients with a genetic variant associated with an AD-AID (5/20 vs 9/100, \( p=0.0419 \); table 4), which is mainly explained through the subgroup of patients with an AP1S3 variant. In particular, consistent with previous association of AP1S3 with pustular psoriasis, this psoriasis form was more commonly diagnosed among the subgroup of patients with an AP1S3 variant (4/5 vs 10/115, \( p<0.0001 \); table 4), which can be largely attributed to the NOD2 variants, which were detected in two out of five patients with Crohn’s disease.

Pharmacological therapies of patients harbouring variants in genes associated with AD-AID ranged from mono-therapy with diverse non-steroidal anti-inflammatory drugs (NSAIDs) to conventional synthetic, targeted or biological disease-modifying antirheumatic drugs (DMARDs) and were similar to the ones employed to treat PsA in patients without such variants (online supplemental table 5). Patients with AD-AID-associated variants displayed higher serum levels of C reactive protein (CRP) levels in patients with AD-AID-associated, indicating higher systemic inflammation that may be consistent with higher activity of PsA. However, rate of escalation/change of pharmacological therapy due to high disease activity was not significantly different between the aforementioned subgroups of patients.
DISCUSSION

The phenotypic spectrum of PsA, its relatively high heritability and the fact that part of its genetic susceptibility is explained through innate immune loci suggested a link between PsA and AIDs. To investigate the latter, we searched for genetic variants in genes associated with monogenic AIDs in a cohort of patients with PsA and identified at least one rare predicted deleterious variant that could account for a monogenic AID in approximately 17% of sequenced patients, especially among patients with pustular psoriasis and IBD. These genetic findings suggest the autoinflammatory aetiology of PsA in this subgroup of patients.

Relatively common were AP1S3 variants, which are associated with pustular psoriasis. AP1S3 encodes a subunit of the adaptor protein complex 1 (AP-1), a heterotetramer mediating vesicular transport between the trans-Golgi network and the endosomes.39 Identified monoallelic variants in AP1S3 have been previously reported to have a loss-of-function effect and cause generalised or palmoplantar pustular psoriasis.34 35 Mechanistically, autoinflammation in case of AP1S3 loss-of-function has been attributed to abnormalities in autophagy, resulting in dysregulated NF-κB activation and consequently increased IL-1 and IL-36α signalling.35 To our knowledge, arthritis had not been previously associated with pathogenic APIS3 variants. In the present study, the frequency of patients with both PsA and pustular psoriasis who harboured a deleterious AP1S3 variant is considerably higher than the previously reported frequency of such variants among patients with pustular psoriasis only (4/14, ie, 28.6% vs 7%–10%), whose evaluation was also based on German and European cohorts.40 41 The latter, together with the identification of a case with a deleterious AP1S3 variant, who had plaque psoriasis only, suggests the strong association of deleterious AP1S3 variants not only with pustular psoriasis, but also with arthritis. However, the role of deleterious APIS3 variants in immune cells that could be relevant for the pathogenesis of arthritis, especially neutrophils that have been shown to display a relatively high APIS3 expression,35 has not been demonstrated yet.

In addition, we have identified four patients with PLCG2 variants. Hypermorphic heterozygous variants in this gene, resulted in hyperactivation of PLCγ2, have been reported to cause multiorgan autoinflammation.37

**Figure 1** Summary of psoriatic manifestations (map, green boxes) and genetic findings (map, blue boxes for variant in genes associated with AD-AIDs and yellow boxes for variants in genes associated with AR-AID) in n=120 patients with PsA; each map column matches a studied patient (upper map summarises findings from patients 1 to 60 and the lower one from 61 to 120). AD-AID, autosomal dominant autoinflammatory disorder; AR-AID, autosomal recessive autoinflammatory disorder; IBD, inflammatory bowel disease; SpA, spondyloarthritis.

**Figure 2** Summary of genes linked to autoinflammatory disorders, whose variations were detected in a cohort of patients with psoriatic arthritis: (A) genes linked to AD-AID and (B) genes linked to AR-AID. Variants in IFIH1 and TREFX were listed under AR-AID, although mutations in either of these genes can also cause AD-AIDs. AD-AID, autosomal dominant autoinflammatory disorder; AR-AID, autosomal recessive autoinflammatory disorder.
Except for arthritis and dermatitis, there was no evidence of interstitial lung disease and ocular inflammation, which are common phenotypic traits of APLAID.\textsuperscript{36, 37} In the four patients with $\text{PLCG2}$ variants, autoinflammation due to gain-of-function variants in $\text{PLCG2}$ has been attributed to an enhanced activation of the NALP3 inflammasome.\textsuperscript{37} However, enhanced IL-1$\beta$ production has been inconsistently reported in patients with APLAID and IL-1 inhibitors have been reported to fail in controlling APLAID-associated autoinflammation.\textsuperscript{37, 42, 43} In several cases, detection of variants in genes associated with autoinflammation could provide an explanation for the form of psoriasis and, in particular, for pustular psoriasis in patients with variants in $\text{CARD14}$ or $\text{AP1S3}$\textsuperscript{34} as well as for extra-articular manifestations, such as aphthous stomatitis in a patient with an $\text{TNFAIP3}$ variant, that may cause A20 haploinsufficiency\textsuperscript{47} or severe deficiencies in B cell activation, transfer experiments in aforementioned mice have demonstrated that cells of myeloid origin primarily account for their inflammatory phenotype, which is consistent with the notion of autoinflammation, although the exact mechanism of inflammation, including involved molecular pathways, have not been investigated yet.

### Table 3: Clinical data of PsA patients with monoallelic mutations in genes associated with AD-IEI/AID

| Patient ID | Age | Sex | IEI/AID gene | Age at first diagnosis of a psoriatic manifestation | First psoriatic manifestation | Psoriatic and other manifestations of immune dysregulation | Current PsA therapy |
|------------|-----|-----|--------------|-----------------------------------------------|-----------------------------|----------------------------------------------------------|---------------------|
| 3          | 70  | F   | NOD2         | 44                            | Psoriasis                   | Plaque psoriasis, asymmetrical oligoarthritis, Crohn’s disease | Secukinumab, MTX     |
| 6          | 67  | F   | NOD2         | 57                            | Psoriasis                   | Plaque psoriasis, polyarthritis                            | MTX                 |
| 11         | 49  | M   | AP1S3        | 19                            | Psoriasis                   | Plaque psoriasis and pustular psoriasis, polyarthritis, enthesitis | Ixequizumab         |
| 12         | 23  | F   | TNFAIP3      | 23                            | Psoriasis                   | Plaque psoriasis, bilateral sacroiliitis, recurrent oral aphthosis | NSAID, prednisolone |
| 13         | 62  | F   | AP1S3        | 24                            | Psoriasis                   | Pustular psoriasis, sacroiliitis, polyarthritis, vitiligo   | Certolizumab pegol, MTX |
| 21         | 33  | F   | COPA         | 18                            | Arthritis                   | Oligoarthritis                                             | MTX, SSZ, NSAID     |
| 22         | 20  | F   | TNFRSF1A     | 14                            | Arthritis                   | Oligoarthritis                                             | Certolizumab        |
| 27         | 52  | F   | PLCG2        | 22                            | Enthesitis                   | Plaque psoriasis, enthesitis, oligoarthritis               | Secukinumab         |
| 39         | 55  | M   | AP1S3        | 33                            | Psoriasis                   | Plaque psoriasis, polyarthritis                            | MTX, NSAID          |
| 57         | 29  | F   | NFKB1        | 3                             | Psoriasis                   | Plaque psoriasis, treatment refractory oligoarthritis      | MTX, NSAID          |
| 64         | 61  | F   | COPA & PLCG2 | 41                            | Psoriasis                   | Plaque psoriasis, oligoarthritis, Crohn’s with fistulas, hypogammaglobulinemia | Infliximab         |
| 65         | 34  | M   | NLRP12       | 29                            | Psoriasis                   | Plaque psoriasis, nail psoriasis, polyarthritis             | Adalimumab, MTX     |
| 70         | 63  | M   | NLRP12       | 49                            | Arthritis                   | Father with psoriasis and PsA, oligoarthritis, bilateral sacroiliitis | Etanercept, MTX |
| 80         | 50  | M   | CARD14 & TNFAIP3 | 46                      | Psoriasis                   | Pustular psoriasis, alopecia areata, enthesitis, oligoarthritis | Tofacitinib         |
| 81         | 53  | M   | NLRP12       | 54                            | Arthritis                   | Plaque psoriasis, polyarthritis                             | MTX                 |
| 86         | 36  | F   | AP1S3        | 20                            | Psoriasis                   | Pustular psoriasis, polyarthritis                           | MTX, prednisolone   |
| 91         | 61  | F   | NOD2, IL1RN  | 51                            | Psoriasis                   | Plaque psoriasis, polyarthritis, Crohn’s disease, coeliac disease, livedo reticularis | Tofacitinib         |
| 98         | 39  | F   | PLCG2, DD5X8 | 37                            | Arthritis                   | Plaque psoriasis, polyarthritis, spondylitis                | MTX                 |
| 115        | 55  | F   | AP1S3        | 46                            | Psoriasis                   | Pustular psoriasis, oligoarthritis, Grave’s disease         | NSAID, prednisolone |
| 116        | 53  | F   | PLCG2        | 50                            | Arthritis                   | Oligoarthritis, hypothyroidism, polyneuropathy, atopic dermatitis, hypogammaglobulinemia | LFN, prednisolone |

F, female; LFN, leflunomide; M, male; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; patient ID, patient identification number; PsA, psoriatic arthritis; SSZ, sulphasalazine.
enterocolitis in a patient with a monoallelic variant in *PLCG2*, which associates with APLAID (table 3)\textsuperscript{37}. In addition to aiding delineation of the clinical heterogeneity of PsA, detection of AD-associated variants and the identification of the autoinflammatory etiology of disease in subgroups of patients might affect strategy to treat PsA and associated manifestations. Despite the modest benefit of treatment with anakinra in patients with PsA,\textsuperscript{48} in cases of disease due to genetic variants that enhance the activation of the NALP3 inflammasome and consequently the production of IL-1β and IL-18, blocking the latter cytokines may represent an attractive therapeutic approach. Further, given the enhanced spontaneous and induced production of IL-36 by keratinocytes from patients with loss-of-function mutations in *AP1S3*, inhibiting IL-36 may represent a therapeutic target, at least to treat pustular psoriasis in these patients.\textsuperscript{35} In case of several genes, including *PLCG2*, which was commonly affected in the present study, elucidation of the pathomechanism of autoimmunization is a prerequisite for the development of a targeted therapy.

Population-based studies revealed a high recurrence risk ratio for PsA among first-degree relatives, resulting in a heritability estimate of more than 80%.\textsuperscript{1,5,6} High heritability of PsA has been explained through genetic factors, which were primarily identified through large-scale GWAS. So far, genetic studies in the field of PsA have been based on the hypothesis-free approach of GWAS, which aims at detecting relatively common variants at a genome-wide level in large populations.\textsuperscript{4,49,50} Genetic alterations identified to confer disease risk through GWAS have suggested the pathogenic relevance of immunological processes, including antigen presentation, cytokines, innate immune pathways and T helper cell differentiation in PsA.\textsuperscript{4,49} With the advent and expanding availability of NGS technologies, the focus of genetic studies has shifted towards rare variants,\textsuperscript{51} which in the field of immunological diseases, led to the discovery of an increasing number of monogenic disorders, falling under IEI, and to the dissection of immunological syndromes, characterised by broad phenotypic variability, into monogenic disorders.\textsuperscript{20} Besides primary immunodeficiency disorders, in case of systemic rheumatic disorders, NGS led to the diagnosis of monogenic forms of SLE,\textsuperscript{32} seronegative vasculitis,\textsuperscript{47,55} chronic polyarthritis\textsuperscript{54} or spondyloarthritis, especially in the subgroup of patients with hypogammaglobulinemia.\textsuperscript{55}

Our study has several limitations. As discussed above, despite using stringent selection criteria, including the rarity and pathogenicity prediction scores, we did not demonstrate the pathogenicity of identified variants, which may lead to an overestimation of the incidence of AID among patients with psoriatic arthritis. However, five patients were identified with previously reported pathogenic variants, all in *AP1S3* and in several cases. As in case of several other groups of IEIs, incomplete penetrance and variable expressivity of reported pathogenic variants questions the strictly monogenic aetiology, suggesting the pathogenic effect of additional genetic modifiers, epigenetic and environmental factors,\textsuperscript{56} which have not been addressed in the present study. Lack of a control group of patients represents a major limitation of our

| Characteristic                        | At least one variant in an AD-AID/IEI-associated gene (n=20) | No variant an AD-AID/IEI-associated gene (n=100) | OR (95% CI) | P value |
|--------------------------------------|---------------------------------------------------------------|-------------------------------------------------|-------------|---------|
| Psoriasis—n (%)                      | 16 (80)                                                       | 80 (80)                                         | 1 (0.3 to 3.32) | 1       |
| Pustular psoriasis—n (%)             | 5 (25)                                                        | 9 (9)                                           | 3.37 (0.99 to 11.44) | 0.0419* |
| Nail psoriasis—n (%)                 | 1 (5)                                                         | 8 (8)                                           | 0.6 (0.07 to 5.13) | 0.64    |
| Oligoarthritis—n (%)                 | 7 (35)                                                        | 24 (24)                                         | 1.7 (0.61 to 4.76) | 1       |
| Polyarthritis—n (%)                  | 9 (45)                                                        | 45 (45)                                         | 1 (0.38 to 2.62) | 1       |
| Axial spondyloarthritis—n (%)        | 4 (20)                                                        | 31 (31)                                         | 0.56 (0.17 to 1.8) | 0.3232  |
| Enthesitis—n (%)                     | 3 (15)                                                        | 32 (32)                                         | 0.4 (0.11 to 1.49) | 0.1620  |
| Anterior uveitis—n (%)               | 0 (0)                                                         | 6 (6)                                           | 0.36 (0.02 to 6.55) | 0.2611  |
| Inflammatory bowel disease—n (%)     | 3 (15)                                                        | 2 (2)                                           | 8.65 (1.34 to 59.67) | 0.0079**|
| Dactylitis—n (%)                     | 1 (5)                                                         | 10 (10)                                         | 0.47 (0.06 to 3.93) | 0.4793  |
| Other autoimmune disorder—n (%)     | 7 (35)                                                        | 29 (29)                                         | 1.32 (0.48 to 3.64) | 0.593   |
| Hashimoto’s thyroiditis              | 0 (0)                                                         | 8 (8)                                           | 0.27 (0.01 to 4.79) | 0.3494  |
| Giant cell arteritis                  | 0 (0)                                                         | 3 (3)                                           | 0.68 (0.03 to 13.67) | 1       |

*p<0.05; **p<0.01.
AD, autosomal dominant; AID, autoinflammatory disorder; IEI, inborn error of immunity; n, number; N, total number.
study. However, the variant filtering strategy employed in the present study included selection of rare variants. Further, high rate of familial cases may have led to selection bias, overestimating the proportion of patients with predicted deleterious variants. Nonetheless, PsA displays high heritability\(^{3,4}\) and the rate of positive family history was comparable to the one reported in previous studies.\(^{27,36}\)

In summary, the identification of genetic variants that are associated with AIDs in patients with PsA provides evidence on the autoimmune inflammatory pathogenesis of PsA. At least in a subgroup of patients with variants in genes linked to AD-AID, PsA could be a manifestation of a monogenic AID.

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