RMD Open

Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Identification of variants in genes associated with autoinflammatory disorders in a cohort of patients with psoriatic arthritis

Faranaz Atschekzei,[1] Natalia Dubrowinskaja,[1] Manfred Anim,[1] Thea Thiele,[2] Torsten Witte,[3] Georgios Sogkas [ID] [1]

Check for updates

[1]Rheumatology and Immunology, Hannover Medical School, Hannover, Germany
[2]Department of Rheumatology and Immunology, Hannover Medical School, Hannover, Germany
[3]Clinical Immunology, Hannover Medical School, Hannover, Germany

Correspondence to
Dr Georgios Sogkas; sogkas.georgios@mh-hannover.de

ABSTRACT

Objectives Besides adaptive immunity genes, genetic risk factors for psoriatic arthritis (PsA) include innate immunity loci, which suggests 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*, *PLCG2, 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Genetic susceptibility to psoriatic arthritis (PsA) is partially explained through innate immune loci, suggesting a link between PsA and autoinflammation.

WHAT THIS STUDY ADDS

⇒ This is the first study evaluating the genetic link between PsA and autoinflammatory disorders (AIDs).
⇒ The identification of genetic variants that associate with AIDs in patients with PsA provides evidence on the autoinflammatory pathomechanism of PsA.
⇒ In the subgroup of patients with variants in genes linked to AIDs, PsA could be a manifestation of a monogenic AID.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study alerts treating physicians for diagnosis of an underlying AID in patients with PsA, especially in case of a coexisting inflammatory bowel disease or pustular psoriasis.
⇒ The autoinflammatory aetiology of PsA may lead to re-evaluation of treatment of both cutaneous and articular inflammation, suggesting innate immunity targets, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interleukin-36 as likely therapeutic targets.

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.[1] Genetic risk factors for PsA partially overlap with the ones of psoriasis.[4] 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.[1 8–11] 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] Variants in genes involved in NF-κB activity, such as in *TNFAIP3*, encoding the protein A20, *NFKBIA*, encoding IκBα, 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 psoriasis 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.[18] 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,[2] the age at onset of first psoriatic manifestation and patients actual and previous treatment.

Targeted NGS
Targeted NGS has been performed as described previously.[26] 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

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.
bDMARD, biological disease-modifying antirheumatic drugs; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; DMARD, disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; IL-17i, interleukin 17 inhibitor; IL-23i, interleukin 23 inhibitor; JAKi, janus kinase inhibitor; n, number; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthritis; TNFi, tumour necrosis factor inhibitor.

criteria has been additionally evaluated with the Sorting Tolerant From Intolerant (SIFT) algorithm,[30] the MutationTaster,[31] Provean[32] and the Human Splicing Finder.[33]

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 χ^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 (ie, 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.[20] 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 *AP1S3* (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 *AP1S3* variants have been previously reported as pathogenic and associated primarily with pustular psoriasis.[34 35] Among patients with PsA harbouring an *AP1S3* 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 Cγ2 (PLCγ2), a signalling mediator primarily expressed by B cells,

Table 2 Monoallelic variants in genes associated with monogenic autoinflammatory disorders or other inborn errors of immunity associated with immune dysregulation, identified in patients with PsA

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	Poly-Phen2 score	Poly-Phen2 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
			NOD2	AD	NC_000016.9	c.2377G>A	p.Val793Met	0.001147	rs104895444	22.000	0.019	0.134	Benign	0.110	T
4	60	F	RNASEH2B	AR	NM_024570.3	c.868G>A	p.Asp290Asn	0.0004186	rs201190805	33.000	0.278	0.987	Probably damaging	0.660	T
6	67	F	NOD2	AD	NC_000016.9	c.1214C>T	p.Ala405Val	0.0001773	rs2076754	22.700	0.019	0.909	Probably damaging	0.050	D
6	67	F	HAVCR2	AR	NM_032782.4	c.830C>T	p.Pro277Leu	0.00788	rs72805186	20.300	3.313	0.265	Benign	0.000	D
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.11T>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	0.230	Benign	0.010	D
13	62	F	AP1S3	AD	NC_000002.11	c.11T>G	p.Phe4Cys	0.007891	rs116107386	34.000	25.600	0.997	Probably damaging	0.000	D
20	52	F	SH3BP2	AR	NC_000004.11	c.724del	p.His242Thrfs*36	0.0001389	rs747250901	25.700	23.900	NA	NA	NA	NA
21	33	F	COPA	AD	NM_001098398.1	c.479G>A	p.Arg160His	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	IL1RN	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	LIG4	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.Met28Leu	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	Probably damaging	0.250	T
31	25	M	HAVCR2	AR	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	0.00007437	rs200017837	35.000	19.330	0.999	Probably damaging	0.030	D

Continued

Table 2 Continued

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	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	rs35960726	23.700	3.313	1.000	Probably damaging	0.250	T
			PSMG2	AR	NC_000018.9	c.467C>A	p.Thr156Lys	0.000004061	rs1373908039	34.000	5.584	0.997	Probably damaging	0.120	T
57	29	F	NFKB1	AD	NM_003998	c.322C>T	p.His108Tyr	0.000006574	rs749065614	27.500	3.313	0.632	Possibly damaging	0.010	D
58	50	F	PSMB9	AR	NC_000006.11	c.548T>C	p.Met183Thr	0.00007498	rs369986248	23.700	12.114	0.084	Benign	NA	NA
61	20	M	RNASEH2B	AR	NM_001142279.2	c.338T>G	p.Leu113Arg	NA	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	rs104895500	28.400	16.710	0.629	Possibly damaging	0.010	D
64	61	F	COPA	AD	NC_000001.10	c.1873A>G	p.Ile625Val	0.00001975	rs539596065	23.200	3.313	0.027	Benign	0.030	D
			PLCG2	AD	NM_002661.3	c.77C>T	p.Thr26Met	0.0005848	rs189301790	24.300	3.313	0.002	Benign	0.020	D
65	34	M	NLRP12	AD	NM_001277126.1	c.616C>T	p.Arg206Cys	0.00008377	rs111754022	23.700	23.600	0.970	Probably damaging	0.130	T
67	55	F	LPIN2	AR	NM_014646.2	c.1510C>T	p.Leu504Phe	0.002562	rs104895500	28.400	16.710	0.629	Possibly damaging	0.010	D
70	63	M	NLRP12	AD	NM_001277126.1	c.910C>T	p.His304Tyr	0.004426	rs141245482	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	rs72556554	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	rs148170776	26.000	0.046	0.859	Possibly damaging	0.570	T
			TNFAIP3	AD	NC_000006.11	c.281C>T	p.Ala94Val	0.00001195	rs776714084	31.000	3.313	0.156	Benign	0.010	D
81	53	M	NLRP12	AD	NM_001277126.1	c.428G>A	p.Arg143His	0.00001194	rs760185291	31.000	23.600	0.945	Probably damaging	0.010	D
86	36	F	AP1S3	AD	NM_001039569.1	c.97C>T	p.Arg33Trp	0.007746	rs138292988	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	rs145588689	23.900	0.500	0.99P8	Probably damaging	0.000	D
91	61	F	IL1RN	AR	NM_001318914.1	c.170G>T	p.Cys57Phe	0.00021	rs201638660	29.000	23.600	0.999	Probably damaging	0.200	T
			NOD2	AD	NC_000016.9	c.485C>T	p.Thr162Met	0.002301	rs61755182	26.000	0.019	0.911	Probably damaging	0.060	T
98	39	F	PLCG2	AD	NM_002661.3	c.1194C>G	p.Ser398Arg	0.000004066	rs1051315426	23.600	3.313	0.090	Benign	NA	NA
			DDX58	AD	NM_014314.3	c.212G>A	p.Arg71His	0.009546	rs72710678	32.000	26.200	0.657	Possibly damaging	0.010	D
115	55	F	AP1S3	AD	NM_001039569.1	c.97C>T	p.Arg33Trp	0.007746	rs138292988	34.000	25.600	0.997	Probably damaging	0.000	D

Continued

Table 2 Continued

Patient ID	Age	Sex	Gene	Inheritance of gene-associated disorder	Refseq transcript	Coding change	Protein change	RS-ID	gnomAD allele freq.	CADD score	MSC-CADD score	Poly-Phen2 score	Poly-Phen2 Pred.	SIFT score	SIFT Pred.
116	53	F	PLCG2	AD	NM_002661.3	c.77C>T	p.Thr26Met	rs189301790	0.0005848	24.300	3.313	0.002	Benign	0.020	D

AD, autosomal dominant; AR, autosomal recessive; CADD, Combined Annotation Dependent Depletion; D, damaging; F, female; freq, frequency; gnomAD, Genome Aggregation Database; MSC, Mutation Significance Cut-off; NA, not available; Patient ID, patient identification number; Pred., prediction; Refseq, reference sequence; SIFT, sorting intolerance from tolerance; T, tolerated.

NK cells and mast cells.[36] Monoallelic gain-of-function mutations in *PLCG2* can cause a rare autoinflammatory syndrome, the autoinflammatory PLCγ2-associated antibody deficiency and immune dysregulation (APLAID), which causes early-onset dermatitis, ocular inflammation, enterocolitis, interstitial lung disease, arthritis and immunodeficiency.[36 37] 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.[38] 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,[34] this psoriasis form was more commonly diagnosed among the subgroup of patients with an *AP1S3* variant (4/5 vs 10/115, p<0.0001). Variants in AD-AID-associated genes were also more frequently detected among the subgroup of PsA patients with Crohn's disease (3/20 vs 2/100, p=0.0079), 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 monotherapy 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.
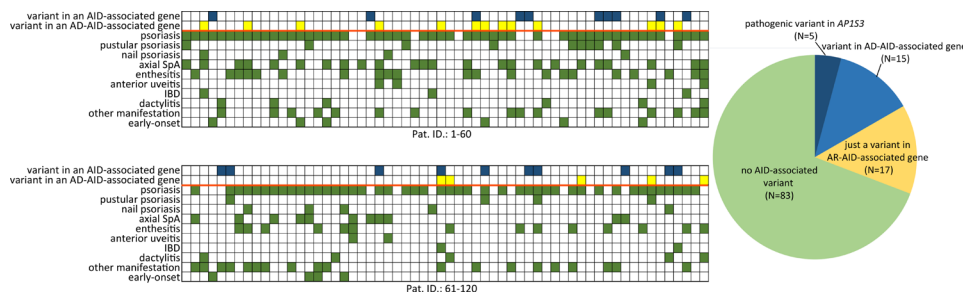
Figure 1 Summary of psoriatic manifestations (map, green boxes) and genetic findings (map, blue boxes for variant in genes associated with AD-AIDs and yellow boxes for variants in genes associated with AR-AID) in n=120 patients with PsA; each map column matches a studied patient (upper map summarises 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.

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 *AP1S3* 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 *AP1S3* variants in immune cells that could be relevant for the pathogenesis of arthritis, especially neutrophils that have been shown to display a relatively high *AP1S3* 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]
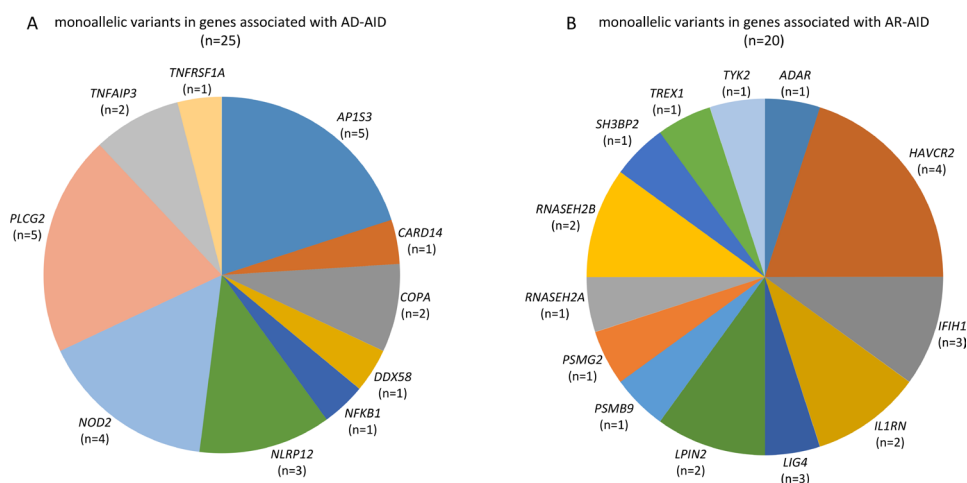

Figure 2 Summary of genes linked to autoinflammatory disorders, whose variations were detected in a cohort of patients with psoriatic arthritis: (A) genes linked to AD-AID and (B) genes linked to AR-AID. Variants in *IFIH1* and *TREX* were listed under AR-AID, although mutations in either of these genes can also cause AD-AIDs. AD-AID, autosomal dominant autoinflammatory disorder; AR-AID, autosomal recessive autoinflammatory disorder.

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	Ixekizumab
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, DDX58	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, sulfasalazine.

Except for arthritis and dermatitis, there was no evidence of interstitial lung disease and ocular inflammation, which are common phenotypic traits of APLAID,[36 37] in the four patients with *PLCG2* variants. Autoinflammation due to gain-of-function variants in *PLCG2* has been attributed to an enhanced activation of the NALP3 inflammasome.[37] However, enhanced IL-1β production has been inconsistently reported in patients with APLAID and IL-1 inhibitors have been reported to fail in controlling ALPAID-associated autoinflammation.[37 42 43] *Plcg2* knock-in mice, which harbour gain-of-function missense mutations in *Plcg2*, display both arthritis and dermatitis,[44 45] which resemble the phenotypic traits of APLAID. Despite the involvement of PLCγ2

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.

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 *CARD14*[46] or *AP1S3*[34] as well as for extra-articular manifestations, such as aphthous stomatitis in a patient with an *TNFAIP3* variant, that may cause A20 haploinsufficiency[47] or severe

Table 4 Characteristics of psoriatic arthritis in patients with and without variants in genes associated with autoinflammatory disorders

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<001.
AD, autosomal dominant; AID, autoinflammatory disorder; IEI, inborn error of immunity; n, number; N, total number.

enterocolitis in a patient with a monoallelic variant in *PLCG2*, which associates with APLAID (table 3).[37] In addition to aiding delineation of the clinical heterogeneity of PsA, detection of AID-associated variants and the identification of the autoinflammatory aetiology 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,[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.[35] In case of several genes, including *PLCG2*, which was commonly affected in the present study, elucidation of the pathomechanism of autoinflammation 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%.[1 56] 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.[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.[4 49] With the advent and expanding availability of NGS technologies, the focus of genetic studies has shifted towards rare variants,[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.[20] Besides primary immunodeficiency disorders, in case of systemic rheumatic disorders, NGS led to the diagnosis of monogenic forms of SLE,[52] seronegative vasculitis,[47 53] chronic polyarthritis[54] or spondyloarthritis, especially in the subgroup of patients with hypogammaglobulinemia.[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,[56] which have not been addressed in the present study. Lack of a control group of patients represents a major limitation of our

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[5 6] and the rate of positive family history was comparable to the one reported in previous studies.[57 58]

In summary, the identification of genetic variants that are associated with AIDs in patients with PsA provides evidence on the autoinflammatory 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.

ORCID iD
Georgios Sogkas http://orcid.org/0000-0003-0855-2945

REFERENCES

1 Schett G, Rahman P, Ritchlin C, *et al*. Psoriatic arthritis from a mechanistic perspective. *Nat Rev Rheumatol* 2022;18:311–25.
2 Pittam B, Gupta S, Harrison NL, *et al*. Prevalence of extra-articular manifestations in psoriatic arthritis: a systematic review and meta-analysis. *Rheumatology* 2020;59:2199–206.
3 Taylor W, Gladman D, Helliwell P, *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
4 O'Rielly DD, Jani M, Rahman P, *et al*. The genetics of psoriasis and psoriatic arthritis. *J Rheumatol* 2019;95:46–50.
5 Pedersen OB, Svendsen AJ, Ejstrup L, *et al*. On the heritability of psoriatic arthritis. disease concordance among monozygotic and dizygotic twins. *Ann Rheum Dis* 2008;67:1417–21.
6 Chandran V, Schentag CT, Brockbank JE, *et al*. Familial aggregation of psoriatic arthritis. *Ann Rheum Dis* 2009;68:664–7.
7 Li Q, Chandran V, Tsoi L, *et al*. Quantifying differences in heritability among psoriatic arthritis (PSA), cutaneous psoriasis (PSC) and psoriasis vulgaris (PsV). *Sci Rep* 2020;10:4925.
8 Haroon M, Winchester R, Giles JT, *et al*. Certain class I HLA alleles and haplotypes implicated in susceptibility play a role in determining specific features of the psoriatic arthritis phenotype. *Ann Rheum Dis* 2016;75:155–62.
9 Winchester R, Minevich G, Steshenko V, *et al*. HLA associations reveal genetic heterogeneity in psoriatic arthritis and in the psoriasis phenotype. *Arthritis Rheum* 2012;64:1134–44.
10 Eder L, Chandran V, Pellet F, *et al*. Human leucocyte antigen risk alleles for psoriatic arthritis among patients with psoriasis. *Ann Rheum Dis* 2012;71:50–5.
11 Prinz JC. Human leukocyte Antigen-Class I alleles and the autoreactive T cell response in psoriasis pathogenesis. *Front Immunol* 2018;9:954.
12 Dolcino M, Lunardi C, Ottria A, *et al*. Crossreactive autoantibodies directed against cutaneous and joint antigens are present in psoriatic arthritis. *PLoS One* 2014;9:e115424.
13 Zhu J, Shi X-F, Chu C-Q. Autoantibodies in psoriatic arthritis: are they of pathogenic relevance? *Chin Med J* 2020;133:2899–901.
14 Stuart PE, Nair RP, Tsoi LC, *et al*. Genome-Wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. *Am J Hum Genet* 2015;97:816–36.
15 Bowes J, Budu-Aggrey A, Huffmeier U, *et al*. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. *Nat Commun* 2015;6:6046.
16 Israel L, Mellett M. Clinical and Genetic Heterogeneity of *CARD14* Mutations in Psoriatic Skin Disease. *Front Immunol* 2018;9:2239.
17 Betrains A, Staels F, Schrijvers R, *et al*. Systemic autoinflammatory disease in adults. *Autoimmun Rev* 2021;20:102774.
18 McDermott MF, Aksentijevich I, Galon J, *et al*. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999;97:133–44.
19 Nigrovic PA, Lee PY, Hoffman HM. Monogenic autoinflammatory disorders: conceptual overview, phenotype, and clinical approach. *J Allergy Clin Immunol* 2020;146:925–37.
20 Tangye SG, Al-Herz W, Bousfiha A, *et al*. Human inborn errors of immunity: 2022 update on the classification from the International Union of immunological societies expert Committee. *J Clin Immunol* 2022. doi:10.1007/s10875-022-01289-3. [Epub ahead of print: 24 Jun 2022].
21 Li WL, Hua LG, Qu P, *et al*. NLRP3 inflammasome: a novel link between lipoproteins and atherosclerosis. *Arch Med Sci* 2016;12:950–8.
22 Martinon F, Pétrilli V, Mayor A, *et al*. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006;440:237–41.
23 Heneka MT, Kummer MP, Stutz A, *et al*. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* 2013;493:674–8.
24 Ambarus C, Yeremenko N, Tak PP, *et al*. Pathogenesis of spondyloarthritis: autoimmune or autoinflammatory? *Curr Opin Rheumatol* 2012;24:351–8.
25 Alperin JM, Ortiz-Fernández L, Sawalha AH. Monogenic lupus: a developing paradigm of disease. *Front Immunol* 2018;9:2496.
26 Sogkas G, Dubrowinskaja N, Schütz K, *et al*. Diagnostic yield and therapeutic consequences of targeted next-generation sequencing in sporadic primary immunodeficiency. *Int Arch Allergy Immunol* 2022;183:337–49.
27 Itan Y, Shang L, Boisson B, *et al*. The mutation significance cutoff: gene-level thresholds for variant predictions. *Nat Methods* 2016;13:109–10.
28 Kircher M, Witten DM, Jain P, *et al*. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet* 2014;46:310–5.
29 Adzhubei IA, Schmidt S, Peshkin L, *et al*. A method and server for predicting damaging missense mutations. *Nat Methods* 2010;7:248–9.
30 Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc* 2009;4:1073–81.

31 Schwarz JM, Cooper DN, Schuelke M, *et al*. MutationTaster2: mutation prediction for the deep-sequencing age. *Nat Methods* 2014;11:361–2.

32 Choi Y, Chan AP. PROVEAN web server: a tool to predict the functional effect of amino acid substitutions and indels. *Bioinformatics* 2015;31:2745–7.

33 Desmet F-O, Hamroun D, Lalande M, *et al*. Human splicing finder: an online bioinformatics tool to predict splicing signals. *Nucleic Acids Res* 2009;37:e67.

34 Setta-Kaffetzi N, Simpson MA, Navarini AA, *et al*. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am J Hum Genet* 2014;94:790–7.

35 Mahil SK, Twelves S, Farkas K, *et al*. AP1S3 mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production. *J Invest Dermatol* 2016;136:2251–9.

36 Wu N, Zhang B, Wang T, *et al*. Case Report: A Rare Case of Autoinflammatory Phospholipase Cγ2 (PLCγ2)-Associated Antibody Deficiency and Immune Dysregulation Complicated With Gangrenous Pyoderma and Literature Review. *Front Immunol* 2021;12:667430.

37 Martín-Nalda A, Fortuny C, Rey L, *et al*. Severe autoinflammatory manifestations and antibody deficiency due to novel hypermorphic PLCG2 mutations. *J Clin Immunol* 2020;40:987–1000.

38 Caso F, Galozzi P, Costa L, *et al*. Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. *RMD Open* 2015;1:e000097.

39 Robinson MS. Adaptable adaptors for coated vesicles. *Trends Cell Biol* 2004;14:167–74.

40 Twelves S, Mostafa A, Dand N, *et al*. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol* 2019;143:1021–6.

41 Mössner R, Wilsmann-Theis D, Oji V, *et al*. The genetic basis for most patients with pustular skin disease remains elusive. *Br J Dermatol* 2018;178:740–8.

42 Chae JJ, Park YH, Park C, *et al*. Connecting two pathways through Ca 2+ signaling: NLRP3 inflammasome activation induced by a hypermorphic PLCG2 mutation. *Arthritis Rheumatol* 2015;67:563–7.

43 Neves JF, Doffinger R, Barcena-Morales G, *et al*. Novel *PLCG2* Mutation in a Patient With APLAID and Cutis Laxa. *Front Immunol* 2018;9:2863.

44 Yu P, Constien R, Dear N, *et al*. Autoimmunity and inflammation due to a gain-of-function mutation in phospholipase C gamma 2 that specifically increases external Ca2+ entry. *Immunity* 2005;22:451–65.

45 Abe K, Fuchs H, Boersma A, *et al*. A novel N-ethyl-N-nitrosourea-induced mutation in phospholipase Cγ2 causes inflammatory arthritis, metabolic defects, and male infertility in vitro in a murine model. *Arthritis Rheum* 2011;63:1301–11.

46 Berki DM, Liu L, Choon S-E, *et al*. Activating CARD14 mutations are associated with generalized pustular psoriasis but rarely account for familial recurrence in psoriasis vulgaris. *J Invest Dermatol* 2015;135:2964–70.

47 Aeschlimann FA, Batu ED, Canna SW, *et al*. A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF-kB-mediated autoinflammatory disease. *Ann Rheum Dis* 2018;77:728–35.

48 Jung N, Hellmann M, Hoheisel R, *et al*. An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). *Clin Rheumatol* 2010;29:1169–73.

49 O'Rielly DD, Rahman P. Genetics of psoriatic arthritis. *Best Pract Res Clin Rheumatol* 2014;28:673–85.

50 Kitsios GD, Zintzaras E. Genome-wide association studies: hypothesis-"free" or "engaged"? *Transl Res* 2009;154:161–4.

51 Momozawa Y, Mizukami K. Unique roles of rare variants in the genetics of complex diseases in humans. *J Hum Genet* 2021;66:11–23.

52 Alperin JM, Ortiz-Fernández L, Sawalha AH. Monogenic lupus: a developing paradigm of disease. *Front Immunol* 2018;9:2496.

53 Meyts I, Aksentijevich I. Deficiency of adenosine deaminase 2 (DADA2): updates on the phenotype, genetics, pathogenesis, and treatment. *J Clin Immunol* 2018;38:569–78.

54 Delmonte OM, Castagnoli R, Calzoni E, *et al*. Inborn errors of immunity with immune dysregulation: from bench to bedside. *Front Pediatr* 2019;7:353.

55 Sogkas G, Dubrowinskaja N, Adriawan IR, *et al*. High frequency of variants in genes associated with primary immunodeficiencies in patients with rheumatic diseases with secondary hypogammaglobulinaemia. *Ann Rheum Dis* 2021;80:392–9.

56 Gruber C, Bogunovic D. Incomplete penetrance in primary immunodeficiency: a skeleton in the closet. *Hum Genet* 2020;139:745–57.

57 Rahman P, Schentag CT, Beaton M, *et al*. Comparison of clinical and immunogenetic features in familial versus sporadic psoriatic arthritis. *Clin Exp Rheumatol* 2000;18:7–12.

58 Solmaz D, Bakirci S, Kimyon G, *et al*. Impact of having family history of psoriasis or psoriatic arthritis on psoriatic disease. *Arthritis Care Res* 2020;72:63–8.