A genome-wide meta-analysis of palmoplantar pustulosis implicates T_H2 responses and cigarette smoking in disease pathogenesis

Ariana Hernandez-Cordero, MSc,[a] Laurent Thomas, PhD,[b,c,d,e] Alice Smail, MPhil,[a] Zhao Qin Lim, MSc,[a,f] Jake R. Saklatvala, PhD,[a] Raymond Chung, MSc,[g] Charles J. Curtis, MRes,[g] Patrick Baum, PhD,[h] Sudha Visvanathan, PhD,[i] A. David Burden, MD,[j] Hywel L. Cooper, BM,[k] Giles Dunnill, MD,[l] Christopher E. M. Griffiths, MD,[m,n] Nick J. Levell, MD,[o] Richard Parslew, MD,[p] Nick J. Reynolds, MD,[q] Shyamal Wahie, MD,[r,s] Richard B. Warren, PhD,[m,t] Andrew Wright, MB ChB,[u,v] the APRICOT and PLUM Study Team, Michael Simpson, PhD,[a] Kristian Hveem, MD, PhD,[c,w] Jonathan N. Barker, MD,[x] Nick Dand, PhD,[a] Mari Løset, PhD,[c,y] Catherine H. Smith, MD,[x] and Francesca Capon, PhD[a]

London, Glasgow, Portsmouth, Bristol, Manchester, Norwich, Liverpool, Newcastle upon Tyne, Durham, Darlington, and Bradford, United Kingdom; Trondheim, Norway; Singapore, Singapore; Biberach, Germany; and Ridgefield, Conn

Background: Palmoplantar pustulosis (PPP) is an inflammatory skin disorder that mostly affects smokers and manifests with painful pustular eruptions on the palms and soles. Although the disease can present with concurrent plaque psoriasis, TNF and IL-17/IL-23 inhibitors show limited efficacy. There is therefore a pressing need to uncover PPP disease drivers and therapeutic targets.

Objectives: We sought to identify genetic determinants of PPP and investigate whether cigarette smoking contributes to disease pathogenesis.

Methods: We performed a genome-wide association meta-analysis of 3 North-European cohorts (n = 1,456 PPP cases and 402,050 controls). We then used the scGWAS program to investigate the cell-type specificity of the association signals. We also undertook genetic correlation analyses to examine the similarities between PPP and other immune-mediated diseases. Finally, we applied Mendelian randomization to analyze the causal relationship between cigarette smoking and PPP.

Results: We found that PPP is not associated with the main genetic determinants of plaque psoriasis. Conversely, we identified genome-wide significant associations with the *FCGR3A/FCGR3B* and *CCHCR1* loci. We also observed 13 suggestive ($P < 5 \times 10^{-6}$) susceptibility regions, including the *IL4/IL13* interval. Accordingly, we demonstrated a significant genetic correlation between PPP and T_H2-mediated diseases such as atopic dermatitis and ulcerative colitis. We also found that genes mapping to PPP-associated intervals were preferentially expressed in dendritic cells and often implicated in T-cell activation pathways. Finally, we undertook a Mendelian randomization analysis, which supported a causal role of cigarette smoking in PPP.

Conclusions: The first genome-wide association study of PPP points to a pathogenic role for deregulated T_H2 responses and cigarette smoking. (J Allergy Clin Immunol 2024;154:657-65.)

Key words: *Palmoplantar pustulosis, genome-wide association study, T_H2, cigarette smoking, Mendelian randomization*

Palmar plantar pustulosis (PPP) is a severe inflammatory skin disorder presenting with neutrophil-filled pustules on the palms and soles.[1] The lesions are painful, disabling, and stigmatizing, so

From [a]the Department of Medical and Molecular Genetics, School of Basic and Medical Biosciences, King's College London, London; [b]the Department of Clinical and Molecular Medicine, [c]HUNT Center for Molecular and Clinical Epidemiology, Department of Public Health and Nursing, and [d]the BioCore-Bioinformatics Core Facility, NTNU-Norwegian University of Science and Technology, Trondheim; [e]the Clinic of Laboratory Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim; [f]the Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore; [g]NIHR BioResource Centre Maudsley, NIHR Maudsley Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust (SLaM) & Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London; [h]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [i]Boehringer Ingelheim Pharmaceuticals, Ridgefield; [j]the School of Infection and Immunity, University of Glasgow, Glasgow; [k]Portsmouth Dermatology Unit, Portsmouth Hospitals Trust, Portsmouth; [l]Bristol Royal Infirmary, Bristol; [m]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester; [n]Department of Dermatology, King's College Hospital, King's College London, London; [o]Norwich Medical School, University of East Anglia, Norwich; [p]the Department of Dermatology, Royal Liverpool Hospitals, Liverpool; [q]the Institute of Cellular Medicine, Medical School, Newcastle University, Newcastle NIHR Biomedical Research Centre and the Department of Dermatology, Royal Victoria Infirmary, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne; [r]University Hospital of North Durham, Durham; [s]Darlington Memorial Hospital, Darlington; [t]the Dermatology Centre, Northern Care Alliance NHS Foundation Trust, Manchester; [u]St Lukes Hospital, Bradford; [v]the Centre for Skin Science, University of Bradford, Bradford; [w]the Department of Innovation and Research, St. Olavs Hospital, Trondheim University Hospital, Trondheim; [x]St John's Institute of Dermatology, School of Basic and Medical Biosciences, King's College London, London; and [y]the Department of Dermatology, Clinic of Orthopedy, Rheumatology and Dermatology, St. Olavs Hospital, Trondheim University Hospital, Trondheim.

Received for publication January 24, 2024; revised April 22, 2024; accepted for publication May 15, 2024.

Available online May 28, 2024.

Corresponding author: Francesca Capon, PhD, 9th Floor, Tower Wing, Guy's Hospital, London SE1 9RT, UK. E-mail: francesca.capon@kcl.ac.uk.

0091-6749

https://doi.org/10.1016/j.jaci.2024.05.015

Abbreviations used
AD: Atopic dermatitis
eQTL: Expression quantitative trait locus
GWAS: Genome-wide association study
LD: Linkage disequilibrium
PPP: Palmoplantar pustulosis
SNP: Single nucleotide polymorphism
UC: Ulcerative colitis

that PPP has a profound impact on quality of life. This is often compounded by comorbidities such as type 1 diabetes, psoriatic arthritis, and Graves' disease.[2] At the same time, PPP remains very difficult to manage, because treatment options are limited by poor efficacy or long-term toxicity.[3]

Because PPP is traditionally classified as a pustular variant of psoriasis, clinical trials have tested several agents used to good effect in plaque psoriasis (TNF, IL-17, and IL-23 blockers) or generalized pustular psoriasis (IL-1 and IL-36 blockers). Such therapeutics, however, showed limited clinical efficacy.[4-7]

These disappointing results reflect an incomplete understanding of pathogenic pathways. Transcription profiling of candidate genes and bulk RNA-sequencing experiments have documented a significant upregulation of T_H17 responses in PPP.[8-10] This was confirmed in a single-cell study recently carried out by our group, which also demonstrated an abnormal activation of T_H2 pathways.[10] It is, however, unclear whether these alterations are a cause or a secondary manifestation of the disease.

PPP disproportionately affects women[11,12] and smokers,[11,12] with evidence of increased disease severity in current versus former/never smokers.[13-15] Although it has been hypothesized that nicotine alters the expression of IL-36 cytokines[14] and anti-inflammatory nicotinic acetylcholine receptors,[16] a causal role of cigarette smoking has not been established.

Genome-wide association studies (GWASs) and Mendelian randomization approaches have unique potential to reveal pathogenic pathways and disease-promoting exposures, especially when applied to large population biobanks.[17] This promise, however, has not been realized in PPP, because the disease is poorly annotated in the UK Biobank (<50 cases reported) and its rarity has hindered the ascertainment of adequately powered data sets.

Here, we have addressed these issues by combining 3 independent Northern European cohorts, including a total of 1,456 cases and 402,050 controls. By undertaking a genome-wide association meta-analysis in this extended data set, we identified 2 genome-wide significant and 13 suggestive susceptibility loci. We then investigated our association results by genetic correlation analysis and Mendelian randomization, implicating T_H2 responses and cigarette smoking in the pathogenesis of PPP.

METHODS

Study cohorts

This work was undertaken according to the principles of the Declaration of Helsinki. Ethical approval was obtained from the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics in Central Norway (reference no. 2015/586), London Bridge Research Ethics Committee, UK (reference no. 16/LO/2190), and the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (reference no. HUS/990/2017). Written informed consent was obtained from all study participants.

Three patient cohorts, originating from the United Kingdom, Norway, and Finland, were examined. The UK data set included 288 affected individuals of European descent, who were recruited in specialist dermatology centers as part of the APRICOT (Anakinra for Pustular Psoriasis: Response in a Controlled Trial) clinical trial[4] and its sister study PLUM (Pustular psoriasis, eLucidating Underlying Mechanisms). All were diagnosed by dermatologists, based on clinical examination and consensus criteria.[18] A total of 7321 unrelated individuals from the English Longitudinal Study of Aging were analyzed as controls.

The Norwegian cases (n = 225) were ascertained from the Trøndelag Health Study (HUNT), a population-based study of adult residents from Trøndelag County.[19] Participant IDs were linked to regional and national health registries, which enabled the identification of PPP cases through the L40.3 (pustulosis palmaris et plantaris) *International Classification of Diseases, Tenth Revision* code. HUNT participants who were not affected by PPP or any other form of psoriasis (n = 64,050) were analyzed as controls.

The Finnish sample was also a population-based cohort. It was derived from the eighth data release of the FinnGen study, a partnership aiming to analyze genome and health data from Finnish biobank participants.[20] Cases (n = 969) were ascertained on the basis of L40.3 *International Classification of Diseases, Tenth Revision* code, and the remaining FinnGen participants (n = 330,975) were analyzed as controls. Key demographic and clinical information for the PPP cases in the 3 cohorts is summarized in Table E1 (in the Online Repository available at www.jacionline.org).

Effect of disease-associated single nucleotide polymorphisms on gene expression

Following single nucleotide polymorphism (SNP) genotyping, imputation, association testing, and meta-analysis (all described in this article's Methods section in the Online Repository at www.jacionline.org), the potential effects of PPP-associated SNPs were investigated. Summary data–based Mendelian randomization was implemented with SMR v1.3.1[21] to determine whether the associated SNP had a causal influence on gene expression. Summary statistics for expression quantitative trait loci (eQTL) identified in non–sun-exposed skin were retrieved from the GTEx database (V7 release, https://gtexportal.org/home/datasets) and examined in conjunction with the PPP meta-analysis results. The genome-wide threshold for statistical significance was set at P less than 9.6×10^{-6} (0.05/5189 gene expression probes examined in the eQTL study). To determine whether gene expression and disease phenotype were influenced by a shared variant (pleiotropy) or multiple variants in linkage disequilibrium (LD) with each other (linkage), a HEIDI test (heterogeneity in dependent instruments) was undertaken. Any SNP generating a statistically significant SMR P value and an HEIDI P value of more than .05 was deemed to have pleiotropic effects on PPP and gene expression.

scRNA-seq–assisted GWAS analysis

We used scGWAS_r1[22] to determine whether the PPP-associated genes identified in the GWAS were concordantly activated in a particular cell type. We first calculated gene-based *P* values by processing the meta-analysis summary statistics with MAGMA[23] (Multi-marker Analysis of GenoMic Annotation). The program aggregates the SNP data available for each gene and implements a multiple regression analysis to test their joint association with the phenotype of interest. Next, we obtained 2 reference scRNA-seq data sets: (1) the PBMC profiles provided by Jia et al[22] (n = 1 donor) and (2) a subset of the healthy PBMC profiles generated by McCluskey et al[10] (n = 3 donors), which we reanalyzed as described in this article's Methods section in the Online Repository. We applied the Box-Cox transformation to the original distribution of $-\log_{10}$ (*P*) from MAGMA and the distribution of log (CPM+1) from the scRNA-seq data sets. Finally, we processed the 2 normalized data sets with scGWAS.

Genetic covariance and pathway enrichment analysis

We used GNOVA (GeNetic cOVariance Analyzer)[24] to investigate pairwise genetic correlations between PPP and traits of interest (plaque psoriasis and 4 diseases where the involvement of T_H2 pathways is well recognized: allergic rhinitis, asthma, atopic dermatitis [AD], and ulcerative colitis [UC]). We retrieved summary statistics from studies shared by the UK Biobank (allergic rhinitis; data set: ukb-b-16499) or published in the literature (all other diseases[25-28]). After removing low-frequency (minor allele frequency < 5%) and palindromic SNPs, we calculated genetic correlations, using the European 1000 Genomes Phase 3[29] (v5) data set as a reference panel for LD estimation. We set the threshold for statistical significance at *P* less than .01 (0.05/5 traits).

For pathway enrichment analyses, we processed GWAS summary statistics with MAGMA to obtain gene-based *P* values. We ranked the output gene list by *P* value and analyzed it with GSEA (Gene Set Enrichment Analysis),[30] using Gene Ontology Biological Process terms as a reference data set. Network analysis and visualization was then undertaken with Cytoscape[31] 3.10.1.

Mendelian randomization

To investigate the causality of cigarette smoking in PPP, Mendelian randomization was implemented with TwoSampleMR v0.5.7[32] in R v.4.3.1. The genetic instrument recapitulating the effects of the exposure was derived from a GWAS for smoking initiation undertaken in 3,383,199 individuals.[33] There was no overlap between the samples from the PPP and smoking GWAS, and the covariates included in the 2 studies (sex, ancestry principal components) were comparable. Variants associated with smoking were clumped to only keep 1 SNP per LD block (LD window = 500 kb, r^2 = 0.01). If a lead SNP from the exposure (smoking) GWAS was not present in the outcome data set (our PPP meta-analysis), a proxy with r^2 more than 0.8 was identified with LDproxy v5.6.3,[34] using the European 1000 Genomes Phase 3 data set as a reference. Finally, palindromic SNPs were removed, and the power of the resulting genetic instrument (n = 238 markers) was validated by calculating the *F* statistic. Because *F* was 38.1, we were able to exclude weak instrument bias (observed when $F < 10$) and implement Mendelian randomization with the inverse variance weighted and weighted median methods. To validate the robustness of our findings, we performed additional tests to examine heterogeneity (inverse variance weighted method), horizontal pleiotropy (Egger intercept), and direction of effect (Steiger test of directionality). A leave-one-out sensitivity analysis was also undertaken.

RESULTS

Genome-wide meta-analysis

To identify genetic determinants of PPP, we undertook a genome-wide association scan of 288 UK cases and 7321 unaffected controls. We then used METAL[35] to meta-analyze our results with those obtained in 2 population-based cohorts analyzed by the HUNT study (225 cases and 64,050 controls) and the FinnGen consortium (969 cases and 330,975 controls). The total data set included 403,506 individuals (1,456 cases and 402,050 controls), genotyped for approximately 9.2M SNPs (see Table E1). Importantly, the distribution of *P* values did not deviate from that expected in the absence of population stratification ($\lambda = 1.05$) (see Fig E1 in this article's Online Repository at www.jacionline.org).

The meta-analysis yielded 2 genome-wide significant loci, spanning *CCHCR1/POU5F1* ($P = 2.9 \times 10^{-11}$) and *FCGR3A/3B* ($P = 1.6 \times 10^{-8}$) (Fig 1; see Fig E2 in this article's Online Repository at www.jacionline.org). Of note, *CCHCR1* maps in close proximity of *HLA-C*0602*, the major genetic determinant of plaque psoriasis.[36] To exclude the possibility that the association we had observed was driven by comorbid plaque psoriasis (reported in 7%-28% of our PPP cases), we examined LD conservation around the *CCHR1* locus. By interrogating population data generated in Finnish and British individuals, we found that the lead SNP in this region was not in LD with rs4406273 ($r^2 < .15$) (see Fig E3 in this article's Online Repository at www.jacionline.org), a well-known *HLA-C*0602* proxy.[37] Accordingly, rs4406273 was not associated with PPP in the FinnGen or UK data set ($P > .05$ for both; no data were available for HUNT where the SNP had not been typed or imputed). Thus, the *CCHCR1* association is independent of *HLA-C*0602*, which is consistent with LD patterns previously described in other data sets.[38]

We next undertook conditional analysis at the *CCHCR1/POU5F1* and *FCGR3A/FCGR3B* loci. We did not detect any secondary association signals, although this may be due to limited statistical power.

Beyond *CCHCR1/POU5F1* and *FCGR3A/FCGR3B*, a further 13 regions showed suggestive evidence for association, with *P* values less than 5×10^{-6} observed in proximity of immune genes such as *IL4*, *HLA-DRA*, and *TNFSF15* (Table I; see Table E2 in this article's Online Repository at www.jacionline.org).

Analysis of genes and cell types underlying association signals

Although the lead SNPs for the *CCHCR1/POU5F1* and *FCGR3A/FCGR3B* loci were in LD with coding variants (rs130068 and rs76714703, respectively; $r^2 > 0.75$ for both), neither of these missense changes was classified as damaging

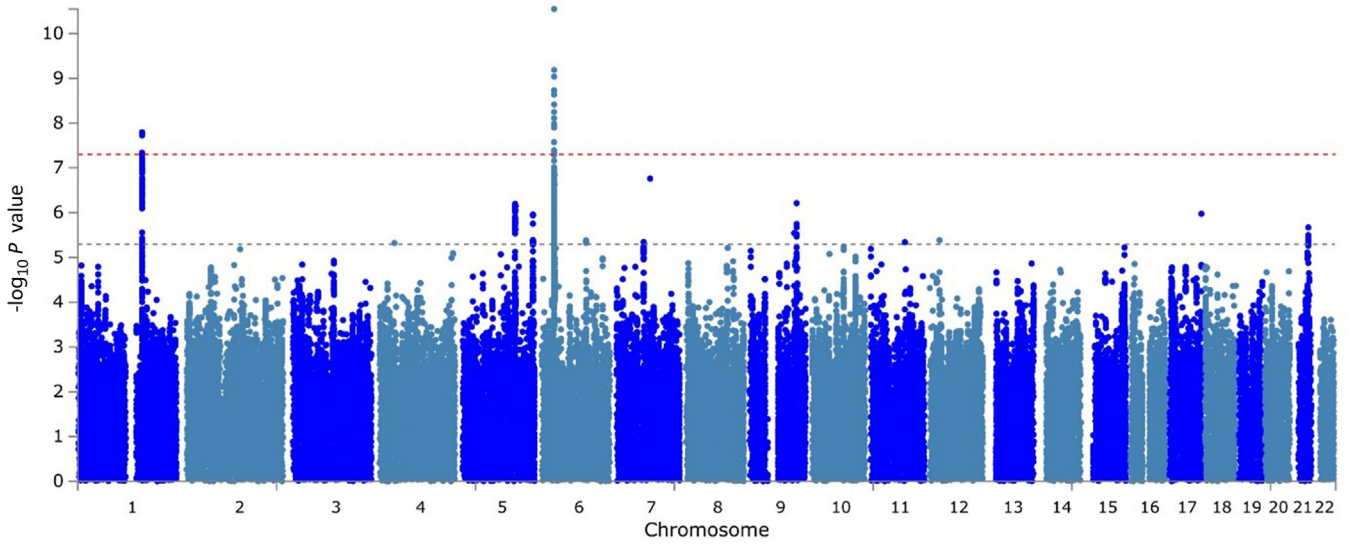

FIG 1. Manhattan plot showing the association signals detected in the GWAS meta-analysis.

by pathogenicity predictors (CADD[39] and MutationTaster[40]). We therefore examined the correlation between the 2 association signals and skin eQTL identified by the GTEx Consortium.[41] Using the SMR program, we found evidence of pleiotropy for SNP rs74538320 in the chromosome 1 locus, indicating that the variant affects both PPP risk and *FCGR3B* expression (pSMR = 5.3×10^{-6}; pHEIDI > 0.05). Conversely, the analysis of the *CCHCR1/POU5F1* locus identified a disease-associated SNP (rs1265079) that is unlikely to directly influence gene expression, but may be in LD with a variant regulating *CCHR1* levels (pSMR = 4.4×10^{-6}; pHEIDI = 4.5×10^{-5}).

We ran a parallel analysis of GTEX blood eQTL, but neither of the above SNPs generated a significant SMR *P* value. Of note, we previously showed that circulating immune cells are likely to play a role in the pathogenesis of PPP.[10] To further investigate our GWAS results in the light of these observations and determine whether the effects of susceptibility alleles were mediated by specific immune populations, we undertook scGWAS analysis.[22] scGWAS derives biological networks that are simultaneously enriched with disease-associated genes and genes that are transcriptionally active in a specific cell type.

Here, we observed that a network centered around *HLA-DRB5*, *CTSH*, and *HLA-DQA2* was enriched for genes that are associated with PPP and expressed in dendritic cells (Fig 2).

Taken together, these post-GWAS analyses indicate that the PPP-associated alleles affect immune pathways in skin and circulating dendritic cells.

Genetic correlation between PPP and T_H2-mediated diseases

To further investigate the pathophysiological relevance of our findings, we used GNOVA to explore genetic correlations between PPP and other immune traits of interest. Given that PPP can present with concurrent plaque psoriasis,[1,13] we first investigated this condition, examining publicly available GWAS summary statistics.[28] However, we did not find any evidence of correlation between PPP and psoriasis. Because we and others have reported T_H2 activation in PPP skin,[8,10] we next examined 4 T_H2-mediated disorders (allergic rhinitis, asthma, AD, and UC). We found that PPP shows a positive correlation with AD ($r = 0.49$; $P = 6.1 \times 10^{-9}$) and an inverse one with UC ($r = -0.20$; $P = 1.5 \times 10^{-4}$).

To validate these observations, we undertook pathway enrichment analyses on the GWAS summary statistics generated in PPP, AD, UC, and psoriasis. Using GSEA, we identified the 50 most significantly enriched Gene Ontology Biological Processes for each disease (false-discovery rate < 0.05). As expected for the analysis of 4 immune-mediated disorders, we observed a substantial overlap between the enriched pathways. Importantly, however, the largest number of shared pathways was observed between PPP and UC (Jaccard similarity index = 0.33) and PPP and AD (Jaccard similarity index = 0.25). A closer inspection of the results revealed that most of the overlapping Gene Ontology processes relate to T-cell differentiation and activation. Conversely, the overlap between PPP and plaque psoriasis (Jaccard similarity index = 0.22) was mostly underpinned by pathways involved in antigen processing/presentation and T-cell cytotoxicity (Fig 3).

Taken together, these observations support a shared genetic basis between PPP and T_H2-mediated diseases.

Mendelian randomization indicates a causal role of cigarette smoking in PPP

Given the high prevalence of smokers among PPP patients,[1,11,13] we next used Mendelian randomization to determine whether cigarette smoking may play a causal role in the disease. We first derived a genetic instrument (n = 238 independent SNPs associated with smoking initiation[33]) recapitulating the exposure to smoking. We then implemented Mendelian randomization using an inverse variance weighted method. This showed a causal influence of the exposure (smoking) on the outcome (PPP) ($P = 3.1 \times 10^{-4}$; odds ratio, 1.52; 95% CI, 1.21-1.92), which was also confirmed with the weighted median method ($P = 3.0 \times 10^{-3}$; odds ratio, 1.63; 95% CI, 1.18-2.25) (see Fig E4 in this article's Online Repository at www.jacionline.org).

TABLE I. Summary of genome-wide significant and suggestive association signals

rsID	Position*	EAF/NEAF	EAF cases	EAF controls	*P* value	OR	95% CI	Direction	Nearest gene†
rs61802325	1:161,588,097	A/G	0.6402	0.6076	1.60×10^{-08}	1.28	1.24- 1.31	+++	*FCGR3B*
rs887467	6:31,141,664	C/G	0.4301	0.4788	2.87×10^{-11}	0.75	0.72- 0.79	−−−	*POU5F1/CCHCR1*
rs73236841	4:37,911,079	A/C	0.7731	0.7905	4.79×10^{-06}	0.78	0.74-0.83	−−−	*TBC1D1*
rs3798130	5:132,042,146	T/C	0.3170	0.3067	6.41×10^{-07}	1.27	1.23-1.31	+++	*KIF3A/IL4*
rs4075959	5:176,784,612	A/G	0.3371	0.3001	1.10×10^{-06}	1.26	1.22-1.30	+++	*RGS14*
rs9487605	6:111,582,885	A/G	0.3970	0.3678	4.15×10^{-06}	1.23	1.19-1.27	+++	*MFSD4B*
rs2097442	6:32,422,191	A/G	0.3238	0.2787	1.43×10^{-07}	1.29	1.24-1.33	+++	*HLA-DRA*
rs10950151	7:68,306,574	T/C	0.0709	0.0566	4.54×10^{-06}	1.54	1.46-1.62	+++	—
rs1990107	7:84,724,076	T/C	0.0407	0.0257	1.75×10^{-07}	2.00	1.88-2.11	+++	*SEMA3D*
rs11793564	9:111,534,315	A/G	0.7523	0.7099	2.87×10^{-06}	1.25	1.21-1.29	+++	*ACTL7B*
rs4246905	9:117,553,249	T/C	0.1913	0.2134	6.16×10^{-07}	0.78	0.73-0.82	−−−	*TNFSF15*
rs9666271	11:85,879,769	T/C	0.9738	0.9624	4.58×10^{-06}	1.64	1.54-1.73	+++	—
rs860876	12:25,158,319	T/G	0.2038	0.1720	4.14×10^{-06}	1.30	1.25-1.35	+++	*IRAG2*
rs112872175	17:80,589,968	G/GATAA	0.2094	0.1843	1.06×10^{-06}	1.31	1.26-1.36	+++	*FOXK2/WDR45B*
rs4817988	21:40,468,838	A/G	0.2184	0.2541	2.15×10^{-06}	0.79	0.75-0.84	−−−	*PSMG1*

− and + refer to protective and risk-bearing effects in individual cohorts.
EA, Effect allele; *EAF*, effect allele frequency; *NEAF*, non–effect allele frequency; *OR*, odds ratio.
*Coordinates refer to GRCh37.
†Nearest gene(s) identified by LocusZoom.

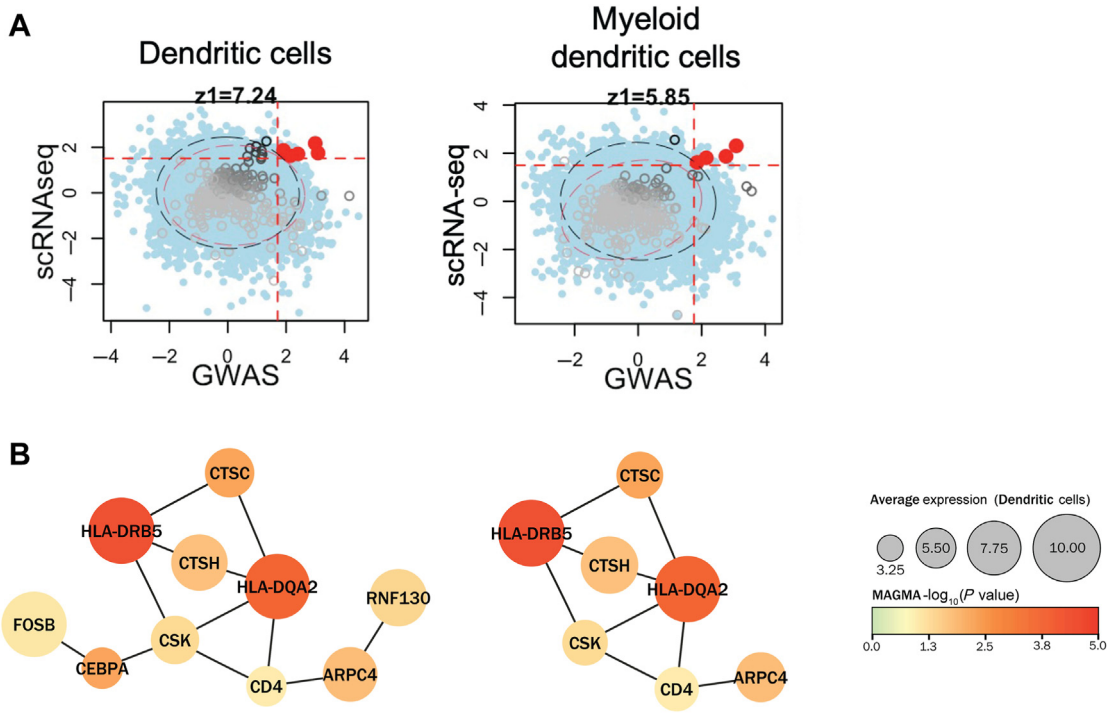

FIG 2. PPP-associated genes are enriched in cell networks (gene modules) that are preferentially expressed in dendritic cells. **A,** The plots show the results obtained using 2 scRNA-seq reference data sets for PBMC gene expression. These were retrieved from the scGWAS package (*left*) and the literature (*right*, see Methods). The plots show the GWAS (x-axis) and scRNA-seq (y-axis) enrichment scores for each module (dots). Real modules are shown in gray, with their CIs indicated by a red circle. Virtual modules, which show the null distribution of module scores, are plotted in blue, with CIs in black. The vertical and horizontal dashed lines indicate the enrichment significance threshold ($z = 1.96$), and significant real modules are highlighted in red. The z1 value illustrates the significance of the red module enrichment. **B,** Network visualization of PPP-associated genes identified from significantly enriched modules in dendritic cells. The graph was generated using gene interaction data retrieved from PathwayCommons.[42] The analysis of the scGWAS package data set identified 5 significant modules with 10 unique genes (*left*), whereas the data set retrieved from the literature yielded 4 significant modules containing 7 unique genes (*right*). In both cases, the most significant module included *CTSH*, *HLA-DQA2*, and *HLA-DRB5*.

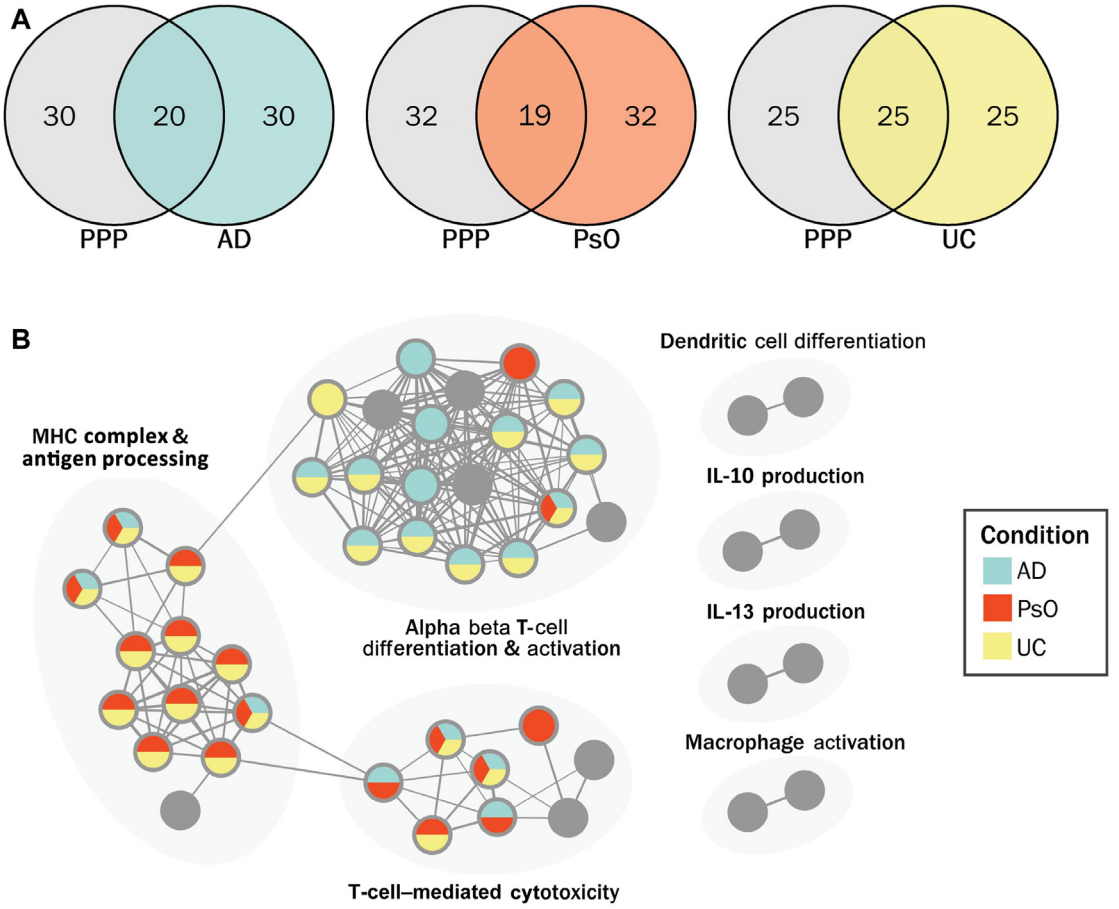

FIG 3. Overlap between GO Biological Process pathways identified from GWAS summary statistics for PPP, plaque psoriasis (PsO), AD, and UC. **A,** Venn diagrams illustrating the overlap between the 50 most significantly enriched pathways identified in each condition. **B,** Cytoscape network analysis of the 50 pathways that are most significantly enriched in PPP. Pathways were clustered using the MCL clusterMaker algorithm and annotated using AutoAnnotate. Each GO pathway is colored to indicate overlap with AD (light blue), PsO (red), and UC (yellow); pathways showing no overlap with AD, PsO, or UC are in gray. *GO*, Gene Ontology.

We tested the robustness of our findings with sensitivity tests measuring heterogeneity between variant causal estimates, horizontal pleiotropy (the phenomenon whereby an SNP may affect the outcome through pathways unrelated to the exposure), and reverse causation. We found no evidence for heterogeneity between variant effects (I^2 = 9%; P > .05) and observed that no SNP had a disproportionate impact on the association between exposure and outcome (see Fig E5 in this article's Online Repository at www.jacionline.org). We also found no evidence for horizontal pleiotropy (P > .05) or reverse causation (Steiger P value < .001). Thus, our genetic instrument is unlikely to violate key Mendelian randomization assumptions, confirming a causal influence of cigarette smoking in PPP.

DISCUSSION

The aim of this study was to identify novel genetic determinants of PPP through the analysis of an extended data set. We therefore ascertained 3 independent case resources and obtained a patient sample of unprecedented size (n = 1456), which enabled us to undertake the first GWAS of PPP.

Our analysis identified 2 genome-wide significant and 13 suggestive susceptibility loci. The associations signals were mostly driven by the FinnGen sample, which accounted for two-thirds (66.2%) of examined cases. Importantly, however, most of the lead SNPs generated P values less than .05 in a second or even a third data set. Moreover, all PPP-associated SNPs showed the same direction of effect across the 3 cohorts. Thus, the final P values reflect a contribution of all data sets, with limited evidence of heterogeneity (Table E2).

One of the genome-wide significant loci maps to the *FCGR* cluster on chromosome 1q23, which spans 5 genes encoding immunoglobulin gamma receptors. Colocalization with skin eQTLs suggested that the association is driven by SNPs downregulating the expression of *FCGR3B*. Interestingly, variation in *FCGR3B* copy number has been associated with susceptibility to SLE and rheumatoid arthritis.[43,44] Disease risk is specifically driven by reduced *FCGR3B* copy number, which is thought to

impair immunoglobulin binding and clearance of immune complexes.[45] Although it is tempting to speculate that a similar mechanism may be at play in PPP, an in-depth dissection of the *FCGR* locus will be required to disentangle the effects of copy number variants and gene eQTLs. The role of the various cell types expressing *FCGR3B* (including T cells, natural killer cells, macrophages, and granulocytes) will also require further investigation. Nonetheless, the association between PPP and *FCGR* genes points to an involvement of antibody-mediated pathways, suggesting an autoimmune component for the pathogenesis of PPP.

The second association signal maps to chromosome 6p21. Although the lead SNP was located within a *POU5F1* intron, our analysis suggested that it may tag an eQTL for the neighboring *CCHCR1* gene. The latter encodes a coiled coil protein that has been implicated in microtubule assembly, centrosome maturation, mRNA metabolism, and cell proliferation.[46] Although a *CCHCR1* coding haplotype has been repeatedly associated with psoriasis susceptibility,[47] the relevant SNPs are not in LD ($r^2 <$ 0.5) with the PPP risk allele identified here. This is in keeping with the lack of association observed for the *HLA-C*0602* proxy rs4406273. Of note, we also obtained negative findings ($P > .05$) for the genomic region encoding *IL36RN*, the main genetic determinant of generalized pustular psoriasis.[48] Thus, PPP is genetically distinct from other comorbid and phenotypically related forms of skin inflammation. In this context, the concurrence of plaque psoriasis in approximately 20% of the examined PPP cases may reflect the activity of shared pathways rather than that of individual genes. This is consistent with the results of our Gene Ontology analysis, which point to the involvement of cytotoxic T cells in both PPP and plaque psoriasis.

Comorbidity between PPP and gluten sensitivity has also been reported.[49] Although we did not observe genome-wide significant or suggestive associations with *HLA-DQB1* variants (the main genetic determinant of celiac disease[49]), we cannot exclude the possibility that such associations may be uncovered by the analysis of larger data sets.

The inspection of suggestive loci revealed that SNPs spanning the *IL4/IL3* gene region, which encodes key T_H2 cytokines, are associated with PPP ($P = 6.4 \times 10^{-7}$ for the lead SNP) as well as AD.[27] In this context, our GNOVA analysis identified a significant correlation between PPP and AD, suggesting a shared genetic risk. Enrichment analyses also showed that the genes that are associated with both conditions preferentially map to T-cell differentiation and T-cell activation pathways. This is in keeping with the notion of a shared T-cell–mediated etiology. The latter is also consistent with the observation that PPP-associated genes are enriched in DC expression modules implicated in T-cell activation.[50,51] Thus, our findings point to a causal role of abnormal T_H2 responses in PPP. This observation has significant implications, given that T_H2 pathways can be targeted by emerging therapeutics, such as IL-4/IL-13 blockers and JAK1 inhibitors.[52] Interestingly, case reports published in recent months suggest that both drug classes could have therapeutic efficacy in PPP.[53,54]

PPP can also occur as a paradoxical reaction to anti-TNF treatment. This phenotype has an innate immune etiology, which is mainly driven by type I interferon overexpression.[55] In fact, neither IL-4 upregulation nor abnormal T-cell infiltration is observed in paradoxical PPP.[55] Thus, our results suggest that the pathogenesis of this condition is distinct from that of classic PPP. To complement our genetic findings, we used Mendelian randomization to show that cigarette smoking has a causal influence on PPP. Interestingly, cigarette smoking is thought to be protective in UC,[56] a condition that showed a negative correlation with PPP in the GNOVA analysis. This suggests that the shared genetic determinants between PPP and UC regulate immune pathways that can be influenced by cigarette smoking. Interestingly, the PPP susceptibility intervals identified in this study do not encompass any of the key genes mediating the inflammatory effects of tobacco smoking (*AHR, AHRR, CYPA1, CYP1B1*). Thus, further studies will be required to mechanistically dissect the effects of smoking in disease pathogenesis.

Our Mendelian randomization results are in keeping with reports that disease severity correlates with cigarette pack years[14] and may improve with smoking cessation.[57,58] The latter observation, however, will require validation in larger patient cohorts, especially as it has recently been reported that smoke has long-lasting effects on adaptive responses.[59] In this context, targeting inflammatory pathways influenced by cigarette smoke may be a more effective therapeutic strategy than smoking cessation alone.

Although ours is by some margin the largest genetic study of PPP, it is still limited by the reliance on core Mendelian randomization assumptions[32] and the relatively small size of the patient sample. The different approaches to case ascertainment (recruitment through Dermatology specialist centers for the UK data set and analysis of *International Classification of Diseases, Tenth Revision* codes for the HUNT and FinnGen studies) may have also generated heterogeneity within the case sample, affecting statistical power. Moreover, our study was based on an analysis of the autosomal genome. Thus, we cannot exclude the possibility that additional disease-associated genes may lie on chromosome X. Of note, such loci could account for the striking preponderance of females among individuals affected by PPP.[11,12] Finally, it is noteworthy that the 3 cohorts underpinning this study were all recruited in Northern Europe. In this context, the inclusion of East Asian cohorts in future meta-analyses will be especially relevant, given the relatively high frequency of PPP in Korea and Japan.[60,61] Thus, larger collaborative consortia will have to be established to generalize our findings to non-European ethnic groups, identify further genetic determinants of PPP, and validate the involvement of pathways that can be targeted by existing therapeutics.

DISCLOSURE STATEMENT

This work was supported by NIHR BioResource Centre Maudsley, National Institute for Health Research Maudsley Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London. We gratefully acknowledge capital equipment funding from the Maudsley Charity (grant no. 980) and Guy's and St Thomas's Charity (grant no. STR130505). The work was also supported by the NIHR Manchester Biomedical Research Centre (grant no. NIHR203308). The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The genotyping in HUNT was financed by the National Institutes of Health; University of Michigan; the Research Council of Norway; the Liaison Committee for Education, Research and Innovation in Central Norway; and the Joint Research

Committee between St Olavs Hospital and the Faculty of Medicine and Health Sciences, NTNU. The APRICOT trial was funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (grant no. EME 13/50/17). This study was supported by Boehringer-Ingelheim and by the Psoriasis Association (grant nos. BSTOP50/5 and PhD studentship ST3/20 to A.H.C.). Z.Q.L. was supported by the Talent Development Fund of KK Women's and Children's Hospital, Singapore. N.J.R. is an NIHR Senior Investigator and is also supported by NIHR Newcastle Biomedical Research Centre, NIHR Newcastle In Vitro Diagnostics Co-operative, and NIHR Newcastle Patient Safety Research Collaboration. The views expressed are those of the author(s) and not necessarily those of the NHS, Department of Health, or King's College London. None of the funders was involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Disclosure of potential conflict of interest: F. Capon has received grants and consultancy fees from Boehringer-Ingelheim. A. D. Burden has received consultancy fees from Boehringer-Ingelheim. C. E. M. Griffiths has received research grants and/or honoraria from AbbVie, Almirall, Anaptysbio, Boehringer-Ingelheim, Bristol Meyers Squibb, Evelo, GlaxoSmithKline, Inmagene, Janssen, Lilly, ONO Pharmaceuticals, Novartis, Pfizer, and UCB. P. Baum and S. Visvanathan are Boehringer-Ingelheim employees. S. Wahie has had nonfinancial support (sponsorship to attend dermatology conferences) from Janssen, AbbVie, Novartis, Almirall, and UCB. J. N. Barker declares paid activities as an advisor and speaker for AbbVie, Amgen, Boehringer-Ingelheim, Bristol Myers Squibb, Johnson & Johnson, Lilly, and Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

We acknowledge the participants and investigators of the FinnGen study. In addition to A. David Burden, Hywell L. Cooper, Giles Dunnil, Christopher E.M. Griffiths, Nick J. Levell, Richard Parslew, Nick J. Reynolds, Shyamal Wahie, Richard B. Warren, Andrew Wright, Jonathan N. Barker, Catherine H. Smith, and Francesca Capon, who are authors, the following APRICOT and PLUM study team members facilitated patient recruitment and data processing for the APRICOT clinical trial and the PLUM study: Thamir Abraham (Peterborough City Hospital, Peterborough), Muhmad Ali (Worthing Hospital, Worthing), Suzannah August (Poole Hospital NHS Foundation Trust, Poole), David Baudry (Guy's Hospital, London), Gabrielle Becher (West Glasgow Ambulatory Care Hospital, Glasgow), Anthony Bewley (Whipps Cross Hospital, Leytonstone), Victoria Brown (St Albans City Hospital, St Albans), Victoria Cornelius (Imperial College London, London), Sharizan Ghaffar (Ninewells Hospital and Medical School, Dundee), John Ingram (University Hospital of Wales, Cardiff), Svetlana Kavakleiva (Royal Lancaster Infirmary, Lancaster), Susan Kelly (The Royal Shrewsbury Hospital, Shrewsbury), Mohsen Khorshid (Basildon Hospital, Essex), Helen Lachmann (Royal Free Hospital, London), Effie Ladoyanni (Russells Hall Hospital, Dudley), Helen McAteer (Psoriasis Association, Northampton), John McKenna (Leicester Royal Infirmary, Leicester), Freya Meynell (Guy's Hospital, London), Prakash Patel (Guy's Hospital, London), Andrew Pink (Guy's Hospital, London), Kingsley Powell (Guy's Hospital, London), Angela Pushparajah (Guy's Hospital, London), Catriona Sinclair (Broomfield Hospital, Essex), and Rachel Wachsmuth (Royal Devon and Exeter NHS Foundation Trust, Exeter).

Clinical implications: The results of the first PPP GWAS support the therapeutic potential of agents that inhibit T_H2 responses and target inflammatory pathways activated by cigarette smoking.

REFERENCES

1. Burden AD, Kirby B. Psoriasis and related disorders. In: Griffiths CEM, Barker JN, Bleiker T, Chalmers RJ, Creamer D, editors. *Rook's textbook of dermatology*. Chichester: Wiley-Blackwell; 2016. pp. 35.1-35.46.
2. Kim DH, Lee JY, Cho SI, Jo SJ. Risks of comorbidities in patients with palmoplantar pustulosis vs patients with psoriasis vulgaris or pompholyx in Korea. JAMA Dermatol 2022;158:650-60.
3. Obeid G, Do G, Kirby L, Hughes C, Sbidian E, Le Cleach L. Interventions for chronic palmoplantar pustulosis: abridged Cochrane systematic review and GRADE assessments. Br J Dermatol 2021;184:1023-32.
4. Cro S, Cornelius VR, Pink AE, Wilson R, Pushpa-Rajah A, Patel P, et al. Anakinra for palmoplantar pustulosis: results from a randomized, double-blind, multicentre, two staged, adaptive placebo controlled trial (APRICOT). Br J Dermatol 2021;186:245-56.
5. Fukasawa T, Yamashita T, Enomoto A, Yoshizaki-Ogawa A, Miyagawa K, Sato S, et al. Optimal treatments and outcome measures of palmoplantar pustulosis: a systematic review and network meta-analysis-based comparison of treatment efficacy. J Eur Acad Dermatol Venereol 2024;38:281-8.
6. Mrowietz U, Bachelez H, Burden AD, Rissler M, Sieder C, Orsenigo R, et al. Secukinumab for moderate-to-severe palmoplantar pustular psoriasis: results of the 2PRECISE study. J Am Acad Dermatol 2019;80:1344-52.
7. Mrowietz U, Burden AD, Pinter A, Reich K, Schakel K, Baum P, et al. Spesolimab, an anti-interleukin-36 receptor antibody, in patients with palmoplantar pustulosis: results of a phase IIa, multicenter, double-blind, randomized, placebo-controlled pilot study. Dermatol Ther (Heidelb) 2021;11:571-85.
8. Baum P, Visvanathan S, Garcet S, Roy J, Schmid R, Bossert S, et al. Pustular psoriasis: molecular pathways and effects of spesolimab in generalized pustular psoriasis. J Allergy Clin Immunol 2022;149:1402-12.
9. Bissonnette R, Nigen S, Langley RG, Lynde CW, Tan J, Fuentes-Duculan J, et al. Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis: results from a randomised controlled trial. J Eur Acad Dermatol Venereol 2014;28:1298-305.
10. McCluskey D, Benzian-Olsson N, Mahil SK, Hassi NK, Wohnhaas CT, et al, APRICOT and PLUM study team. Single-cell analysis implicates TH17-to-TH2 cell plasticity in the pathogenesis of palmoplantar pustulosis. J Allergy Clin Immunol 2022;150:882-93.
11. Assan F, Husson B, Hegazy S, Seneschal J, Aubin F, Mahe E, et al. Palmoplantar pustulosis and acrodermatitis continua of Hallopeau: demographic and clinical comparative study in a large multicentre cohort. J Eur Acad Dermatol Venereol 2022;36:1578-83.
12. Twelves S, Mostafa A, Dand N, Burri E, Farkas K, Wilson R, et al. Clinical and genetic differences between pustular psoriasis subtypes. J Allergy Clin Immunol 2019;143:1021-6.
13. Benzian-Olsson N, Dand N, Chaloner C, Bata-Csorgo Z, Borroni R, Burden AD, et al. Association of clinical and demographic factors with the severity of palmoplantar pustulosis. JAMA Dermatol 2020;156:1216-22.
14. Kobayashi K, Kamekura R, Kato J, Kamiya S, Kamiya T, Takano K, et al. Cigarette smoke underlies the pathogenesis of palmoplantar pustulosis via an IL-17A-induced production of IL-36gamma in tonsillar epithelial cells. J Invest Dermatol 2021;141:1533-41.e4.
15. Sarikaya Solak S, Kara Polat A, Kilic S, Oguz Topal I, Saricaoglu H, Karadag AS, et al. Clinical characteristics, quality of life and risk factors for severity in palmoplantar pustulosis: a cross-sectional, multicentre study of 263 patients. Clin Exp Dermatol 2022;47:63-71.
16. Hagforsen E, Edvinsson M, Nordlind K, Michaelsson G. Expression of nicotinic receptors in the skin of patients with palmoplantar pustulosis. Br J Dermatol 2002;146:383-91.
17. Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafo MR, et al. *Mendelian randomization*. Nat Rev Methods Primers 2022;2(6).
18. Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Koks S, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 2017;31:1792-9.
19. Brumpton BM, Graham S, Surakka I, Skogholt AH, Loset M, Fritsche LG, et al. The HUNT study: a population-based cohort for genetic research. Cell Genom 2022;2:100193.
20. Kurki MI, Karjalainen J, Palta P, Sipila TP, Kristiansson K, Donner KM, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature 2023;613:508-18.
21. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet 2016;48:481-7.
22. Jia P, Hu R, Yan F, Dai Y, Zhao Z. scGWAS: landscape of trait-cell type associations by integrating single-cell transcriptomics-wide and genome-wide association studies. Genome Biol 2022;23:220.

23. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol 2015;11:e1004219.
24. Lu Q, Li B, Ou D, Erlendsdottir M, Powles RL, Jiang T, et al. A powerful approach to estimating annotation-stratified genetic covariance via GWAS summary statistics. Am J Hum Genet 2017;101:939-64.
25. de Lange KM, Moutsianas L, Lee JC, Lamb CA, Luo Y, Kennedy NA, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. Nat Genet 2017;49:256-61.
26. Ferreira MAR, Mathur R, Vonk JM, Szwajda A, Brumpton B, Granell R, et al. Genetic architectures of childhood- and adult-onset asthma are partly distinct. Am J Hum Genet 2019;104:665-84.
27. Sliz E, Huilaja L, Pasanen A, Laisk T, Reimann E, Magi R, et al. Uniting biobank resources reveals novel genetic pathways modulating susceptibility for atopic dermatitis. J Allergy Clin Immunol 2022;149:1105-12.e9.
28. Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nat Genet 2012;44:1341-8.
29. The 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, et al. A global reference for human genetic variation. Nature 2015;526:68-74.
30. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci U S A 2005; 102:15545-50.
31. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003;13:2498-504.
32. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018;7:e34408.
33. Saunders GRB, Wang X, Chen F, Jang SK, Liu M, Wang C, et al. Genetic diversity fuels gene discovery for tobacco and alcohol use. Nature 2022; 612:720-4.
34. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. Bioinformatics 2015;31:3555-7.
35. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genome-wide association scans. Bioinformatics 2010;26:2190-1.
36. Tsoi LC, Stuart PE, Tian C, Gudjonsson JE, Das S, Zawistowski M, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun 2017;8:15382.
37. Stuart PE, Tejasvi T, Shaiq PA, Kullavanijaya P, Qamar R, Raja GK, et al. A single SNP surrogate for genotyping HLA-C*06:02 in diverse populations. J Invest Dermatol 2015;135:1177-80.
38. Veal CD, Capon F, Allen MH, Heath EK, Evans JC, Jones A, et al. Family-based analysis using a dense single-nucleotide polymorphism-based map defines genetic variation at PSORS1, the major psoriasis-susceptibility locus. Am J Hum Genet 2002;71:554-64.
39. Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. CADD: predicting the deleteriousness of variants throughout the human genome. Nucleic Acids Res 2019;47:D886-94.
40. Schwarz JM, Rodelsperger C, Schuelke M, Seelow D. MutationTaster evaluates disease-causing potential of sequence alterations. Nat Methods 2010;7:575-6.
41. GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science 2020;369:1318-30.
42. Rodchenkov I, Babur O, Luna A, Aksoy BA, Wong JV, Fong D, et al. Pathway Commons 2019 Update: integration, analysis and exploration of pathway data. Nucleic Acids Res 2020;48:D489-97.
43. Mueller M, Barros P, Witherden AS, Roberts AL, Zhang Z, Schaschl H, et al. Genomic pathology of SLE-associated copy-number variation at the FCGR2C/FCGR3B/FCGR2B locus. Am J Hum Genet 2013;92:28-40.
44. Rahbari R, Zuccherato LW, Tischler G, Chihota B, Ozturk H, Saleem S, et al. Understanding the genomic structure of copy-number variation of the low-affinity Fcgamma receptor region allows confirmation of the association of FCGR3B deletion with rheumatoid arthritis. Hum Mutat 2017;38:390-9.
45. Nossent JC, Becker-Merok A, Rischmueller M, Lester S. Susceptibility for lupus nephritis by low copy number of the FCGR3B gene is linked to increased levels of pathogenic autoantibodies. Autoimmune Dis 2013;2013:750814.
46. Tervaniemi MH, Katayama S, Skoog T, Siitonen HA, Vuola J, Nuutila K, et al. Intracellular signalling pathways and cytoskeletal functions converge on the psoriasis candidate gene CCHCR1 expressed at P-bodies and centrosomes. BMC Genomics 2018;19:432.
47. Asumalahti K, Veal C, Laitinen T, Suomela S, Allen M, Elomaa O, et al. Coding haplotype analysis supports HCR as the putative susceptibility gene for psoriasis at the MHC PSORS1 locus. Hum Mol Genet 2002;11:589-97.
48. Hussain S, Berki DM, Choon SE, Burden AD, Allen MH, Arostegui JI, et al. IL36RN mutations define a severe auto-inflammatory phenotype of generalized pustular psoriasis. J Allergy Clin Immunol 2015;135:1067-70.
49. Michaelsson G, Kristjansson G, Pihl Lundin I, Hagforsen E. Palmoplantar pustulosis and gluten sensitivity: a study of serum antibodies against gliadin and tissue transglutaminase, the duodenal mucosa and effects of gluten-free diet. Br J Dermatol 2007;156:659-66.
50. Wildner G, Kaufmann U. What causes relapses of autoimmune diseases? The etiological role of autoreactive T cells. Autoimmun Rev 2013;12:1070-5.
51. Zhu S, Wang H, Ranjan K, Zhang D. Regulation, targets and functions of CSK. Front Cell Dev Biol 2023;11:1206539.
52. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. Nat Rev Drug Discov 2022;21:21-40.
53. Gleeson D, Barker J, Capon F, Pink AE, Woolf RT, Smith CH, et al. Are Janus kinase inhibitors an effective treatment for palmoplantar pustulosis? A critically appraised topic. Br J Dermatol 2023;188:471-3.
54. Zheng YX, Chen XB, Wang ZY, Cai SQ, Zheng M, Koh LF, et al. Efficacy of dupilumab in palmoplantar pustulosis treatment highlights the role of Th2 inflammation. Allergy 2024;79:1361-4.
55. Conrad C, Di Domizio J, Mylonas A, Belkhodja C, Demaria O, Navarini AA, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. Nat Commun 2018;9:25.
56. Piovani D, Pansieri C, Kotha SRR, Piazza AC, Comberg CL, Peyrin-Biroulet L, et al. Ethnic differences in the smoking-related risk of inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis 2021;15: 1658-78.
57. Michaelsson G, Gustafsson K, Hagforsen E. The psoriasis variant palmoplantar pustulosis can be improved after cessation of smoking. J Am Acad Dermatol 2006;54:737-8.
58. Mrowietz U, van de Kerkhof PC. Management of palmoplantar pustulosis: do we need to change? Br J Dermatol 2011;164:942-6.
59. Saint-Andre V, Charbit B, Biton A, Rouilly V, Posseme C, Bertrand A, et al. Smoking changes adaptive immunity with persistent effects. Nature 2024;626: 827-35.
60. Lee JY, Kang S, Park JS, Jo SJ. Prevalence of psoriasis in Korea: a population-based epidemiological study using the Korean National Health Insurance Database. Ann Dermatol 2017;29:761-7.
61. Ramcharran D, Strober B, Gordon K, DeKlotz C, Fakharzadeh S, Yang YW, et al. The epidemiology of palmoplantar pustulosis: an analysis of multiple health insurance claims and electronic health records databases. Adv Ther 2023;40: 5090-101.

METHODS

Genotyping and data quality control

The UK PPP samples were typed on an Infinium Global Screening Array 24 v3.0 (Illumina, San Diego, Calif) and genotypes were called with GenomeStudio v2.0.50 (Illumina). For sample quality control (QC), individuals were excluded from further analysis if they had less than 99% genotype calls, their genotypes did not match the reported sex, they had a high kinship coefficient (>0.088) with another study participant, or a heterozygosity ratio deviating by more than 3 SDs from the mean. For genotype QC, SNPs with Hardy-Weinberg equilibrium P values less than 10^{-10}, call rates less than 99%, or minor allele frequency less than 1% were excluded.

Control UK genotypes from the English Longitudinal Study of Ageing cohort (previously generated on lllumina HumanOmni2.5-4v1 and HumanOmni2.5-8v1.3 arrays) were retrieved from the European Phenome-genome archive (https://ega-archive.org/) and subjected to the quality control steps described above. Cases and controls were then merged, and principal-component analysis was implemented to exclude individuals of non-European descent.

Norwegian participants from the HUNT2 (1995-1997) and HUNT3 (2006-2008) cohorts were genotyped using HumanCoreExome12 v1.0, HumanCoreExome12 v1.1, or UM HUNT Biobank v1.0 Illumina arrays. Genotypes were called with GenomeStudio v.2011.1 (Illumina). Samples with less than 99% genotype calls, large copy number variants, or more than 2.5% contamination (as estimated with BAF Regress[E1]) were excluded. Individuals of non-European ancestry were also removed, alongside those with X chromosome genotypes that did not match the recorded sex. Rare genetic variants (minor allele frequency < 1%) and those out of Hardy-Weinberg equilibrium (P < .0001) were excluded.

The FinnGen samples (r8 release) had been typed on Illumina or Affymetrix custom arrays, with calls derived using GenCall/zCall (Illumina) for the former and AxiomGT1 (Applied Biosystems) for the latter. For sample QC, individuals were excluded from further analysis if their genotype did not match the recorded sex, genotype missingness was more than 5%, heterozygosity deviated from the mean by more than 4 SDs, or non-Finnish ancestry was detected. For genotype QC, variants with call rates less than 98%, Hardy-Weinberg equilibrium P values less than 10^{-6}, or minor allele count less than 3 were excluded.

Imputation and genome-wide association analysis

For the UK data set, the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html#!) was used to phase SNPs with Eagle 2.3[E2] and impute genotypes with Minimac4 v4.1.2.[E3] The European 1000 Genomes Phase 3 (v5) data set was selected as a reference panel. The GWAS was undertaken with PLINK 1.94.1.[E4] A logistic regression model was applied whereby sex and the first 10 ancestry principal components (PCs) were analyzed as covariates and genotype probabilities (dosages) were used for imputed variants.

For the HUNT study, imputation was performed by phasing SNPs with EAGLE v 2.3 and imputing genotypes using either (1) Minimac3 v2.0. and using a reference panel constructed from Haplotype Reference Consortium genotypes (release v1.1) and whole-genome sequences of 2202 HUNT participants or (2) Minimac4 v1.0.2 and using the European 1000 Genomes Phase 3 (version 5) data set as a reference panel. The GWAS was run by fitting a logistic mixed model with SAIGE v0.35.8.3,[E5] using sex, birth year, genotyping batch, and 4 ancestry PCs as covariates. Genotype dosages were used for imputed variants. All analyses were performed in digital labs at HUNT Cloud, NTNU - Norwegian University of Science and Technology, Trondheim, Norway.

For the FinnGen data set, imputation was carried using Beagle 4.1[E6] and a population-specific reference panel (Sequencing Initiative Suomi v3, based on whole-genome sequences of 3775 Finnish individuals), as described elsewhere.[E7] The GWAS was implemented with SAIGE v0.35.8.8, using sex, age, genotyping batch, and 10 PCs as covariates. Summary statistics were made publicly available and were retrieved for this study through the FinnGen portal (www.finngen.fi/en/access_results).

Meta-analysis, conditional analysis, and LD estimates

A total of 9,168,215 SNPs present in all 3 data sets and aligned to the same reference allele were analyzed in 1,456 cases and 402,050 controls. METAL[E8] v2011.03.25 was used to perform a meta-analysis weighted for effective sample size. Given the small number of data sets and the resulting difficulty in estimating the variance between studies, a fixed-effect model was selected. The associations yielding P values less than 5.0×10^{-8} were considered genome-wide significant, whereas those generating P values less than 5×10^{-6} were deemed suggestive. The quantile-quantile plot, Manhattan plot, and regional association plots were generated with FUMA v1.5.4.[E9]

Conditional analysis was performed with GCTA-COJO[E10] v1.94.1, using the UK cohort as a reference sample for LD estimation. P values less than 5×10^{-8} were considered genome-wide significant.

LD conservation across the 130-kb region spanning *HLA-C, CCHCR1*, and *PSORS1C3* was assessed using the 1000 Genomes Phase 3 genotypes for British and Finnish participants (GBR and FIN data sets). r^2 correlation coefficients were calculated for all pairs of common SNPs, and the results were visualized using Haploview v4.2.0.[E11]

PBMC scRNA-seq reanalysis

scRNA-seq raw counts were retrieved for 3 of the healthy PBMC samples analyzed by McCluskey et al[E12] (subseries GSE185857; sample IDs: HC11, HC13, and HC14) and imported in Seurat v4.3.0.[E13] Cells with less than 300 or more than 5000 gene counts were excluded, alongside cells with more than 20% mitochondrial gene reads. The 3 filtered data sets were merged and integrated in a single Seurat object. The data were normalized and then scaled. Following PC analysis, k-nearest neighborhoods were defined and unsupervised clustering was performed with a resolution of 0.4. The cell clusters were visualized using uniform manifold approximation projection and annotated on the basis of expression of canonical marker genes.

REFERENCES

E1. Jun G, Flickinger M, Hetrick KN, Romm JM, Doheny KF, Abecasis GR, et al. Detecting and estimating contamination of human DNA samples in sequencing and array-based genotype data. Am J Hum Genet 2012;91:839-48.

E2. Loh PR, Danecek P, Palamara PF, Fuchsberger C, A Reshef Y, K Finucane H, et al. Reference-based phasing using the Haplotype Reference Consortium panel. Nat Genet 2016;48:1443-8.

E3. Das S, Forer L, Schonherr S, Sidore C, Locke AE, Kwong A, et al. Next-generation genotype imputation service and methods. Nat Genet 2016;48: 1284-7.

E4. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 2015;4:7.

E5. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat Genet 2018;50:1335-41.

E6. Browning BL, Zhou Y, Browning SR. A one-penny imputed genome from next-generation reference panels. Am J Hum Genet 2018;103:338-48.

E7. Kurki MI, Karjalainen J, Palta P, Sipila TP, Kristiansson K, Donner KM, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature 2023;613:508-18.

E8. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26:2190-1.

E9. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. Nat Commun 2017;8:1826.

E10. Yang J, Ferreira T, Morris AP, Medland SE, Genetic Investigation of ATC, Replication DIG, et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. Nat Genet 2012; 44:369-75, S1-3.

E11. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263-5.

E12. McCluskey D, Benzian-Olsson N, Mahil SK, Hassi NK, Wohnhaas CT, Apricot, et al. Single-cell analysis implicates TH17-to-TH2 cell plasticity in the pathogenesis of palmoplantar pustulosis. J Allergy Clin Immunol 2022;150:882-93.

E13. Stuart T, Butler A, Hoffman P, Hafemeister C, Papalexi E, Mauck WM III, et al. Comprehensive integration of single-cell data. Cell 2019;177:1888-902.e21.

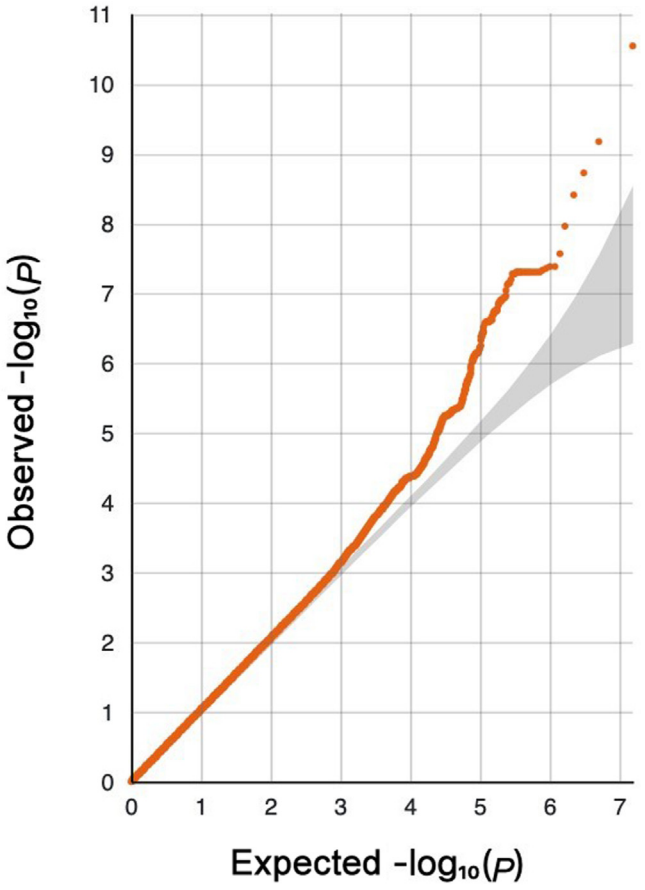

FIG E1. Meta-analysis quantile-quantile plot showing that the distribution of *P* values did not significantly deviate from that expected under the null hypothesis (shaded in gray).

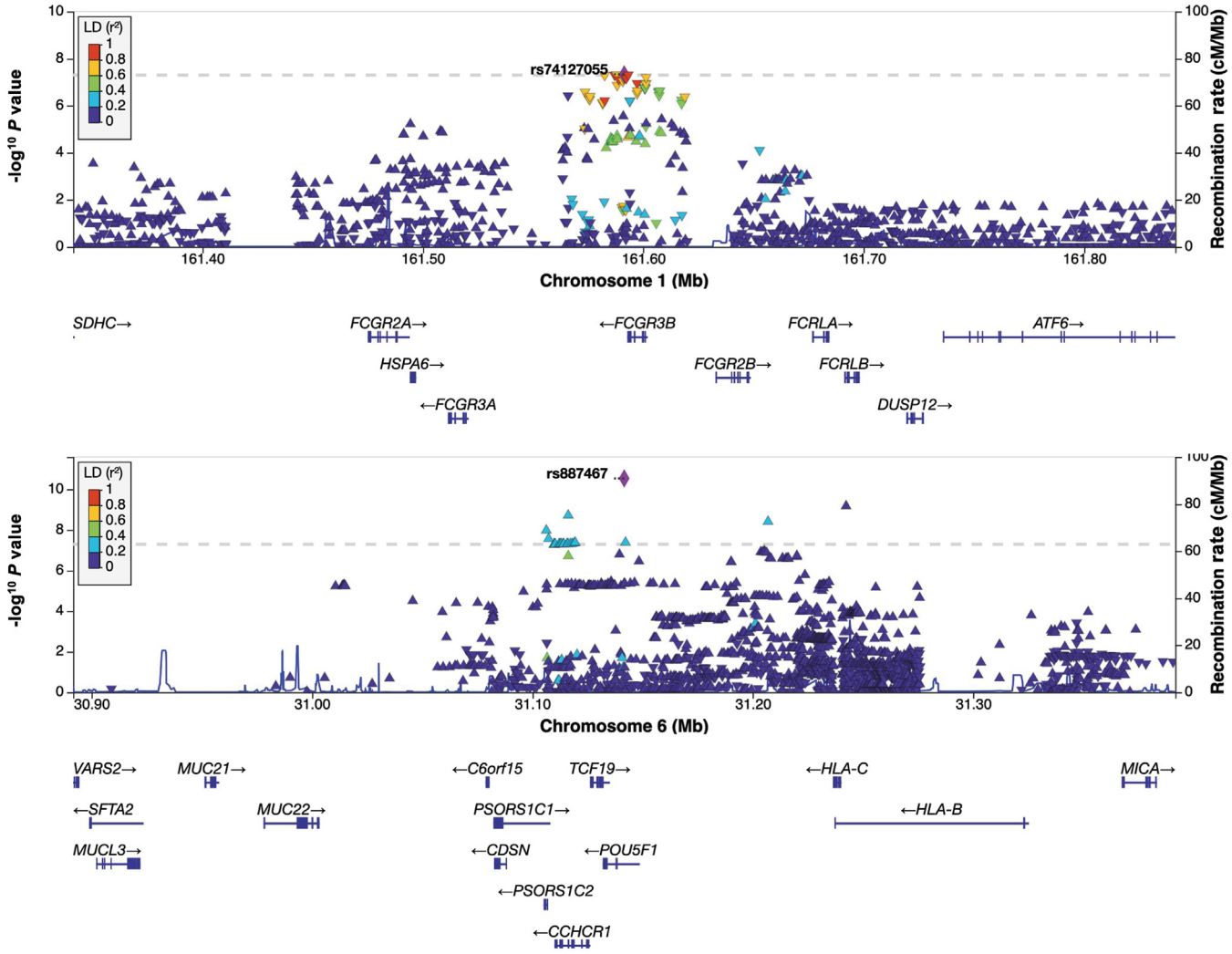

FIG E2. Regional association plots for the 1q23 and 6p21 susceptibility loci. *P* values and recombination rates are plotted against chromosomal coordinates and gene positions.

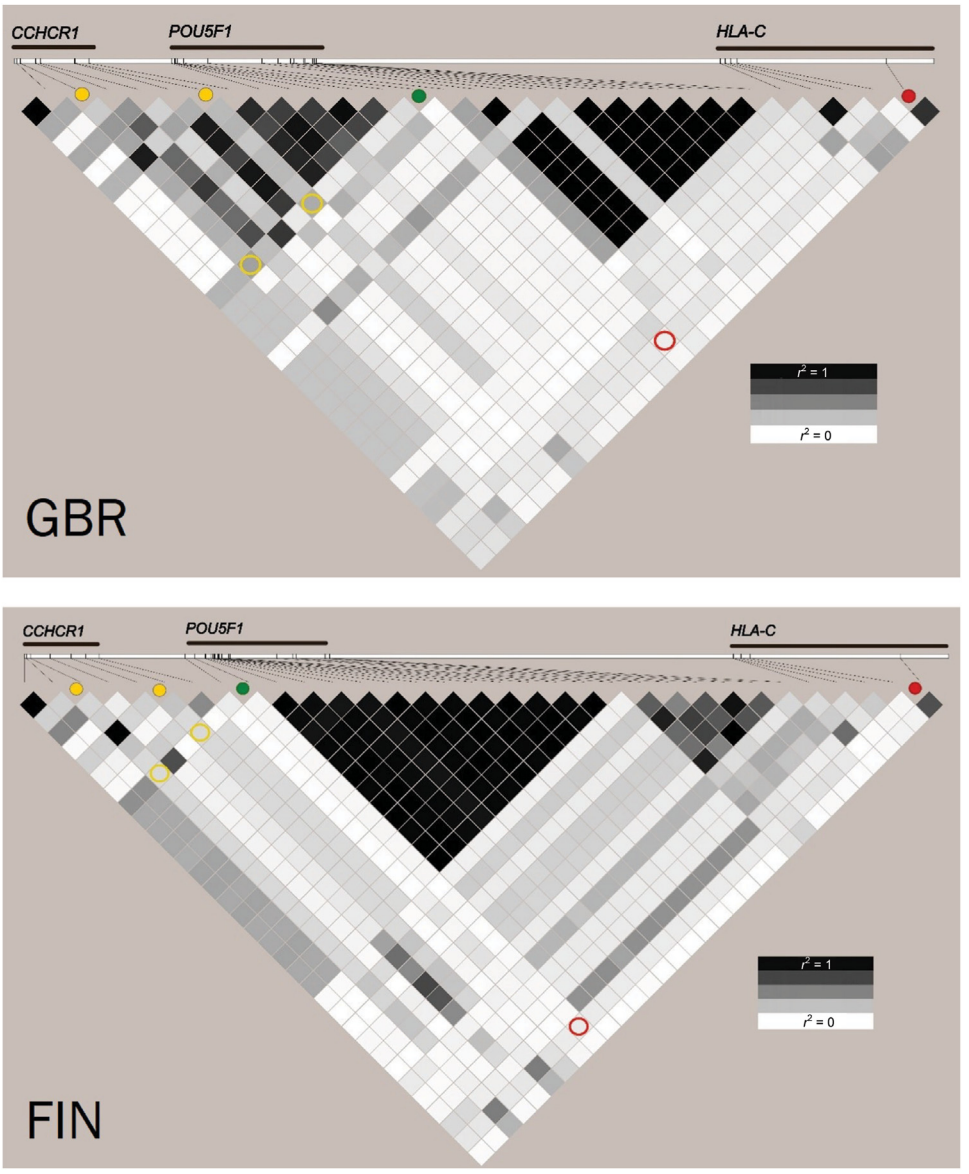

FIG E3. LD conservation plots showing pairwise r^2 between SNPs genotyped by the 1000 Genomes Project in British (GBR) and Finnish (FIN) individuals. The white bar at the top of each plot illustrates the position of the examined SNP with respect to *CCHCR1*, *POU5F1*, and *HLA-C*. The colored circles show that the lead SNP from the 6p21 region (green dot) is not in LD with the *HLA-Cw*0602* proxy SNP (red dot) or the *CCHCR1* SNPs previously associated with psoriasis (yellow dots).

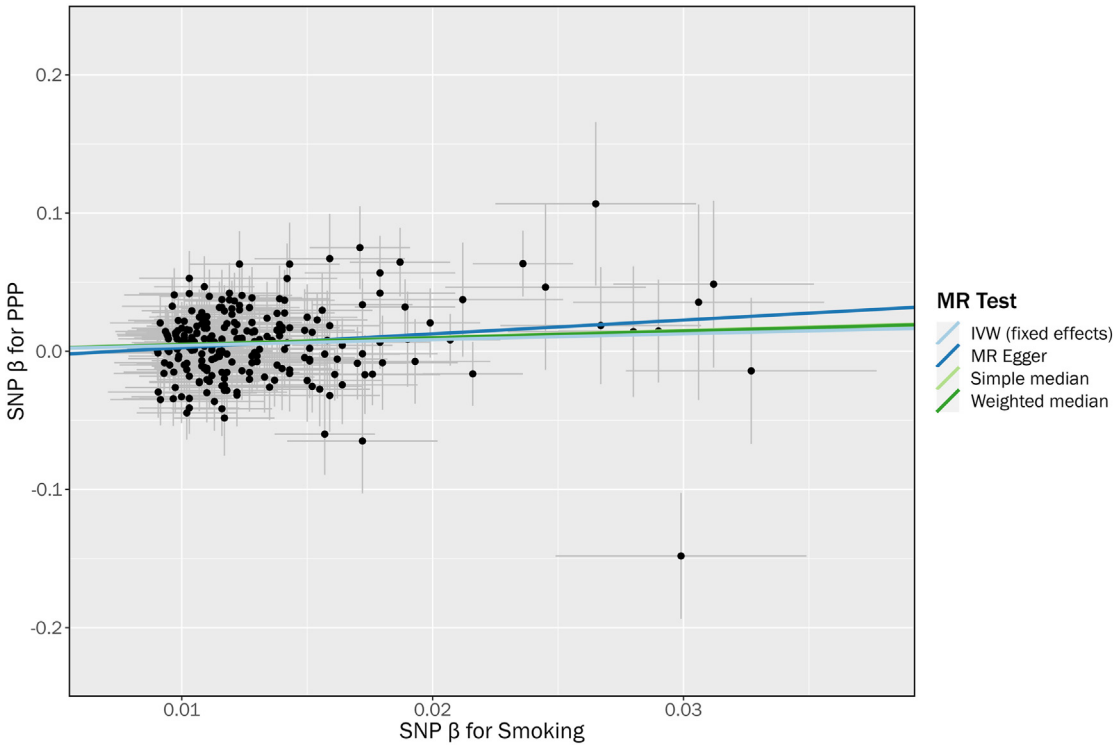

FIG E4. Results of Mendelian randomization. MR scatter plot for the effect of smoking (exposure) on PPP (outcome). A genetically predicted increase in the likelihood of smoking initiation was associated with increased risk of PPP. The slope of each line corresponds to the causal effect estimated with the relevant method.

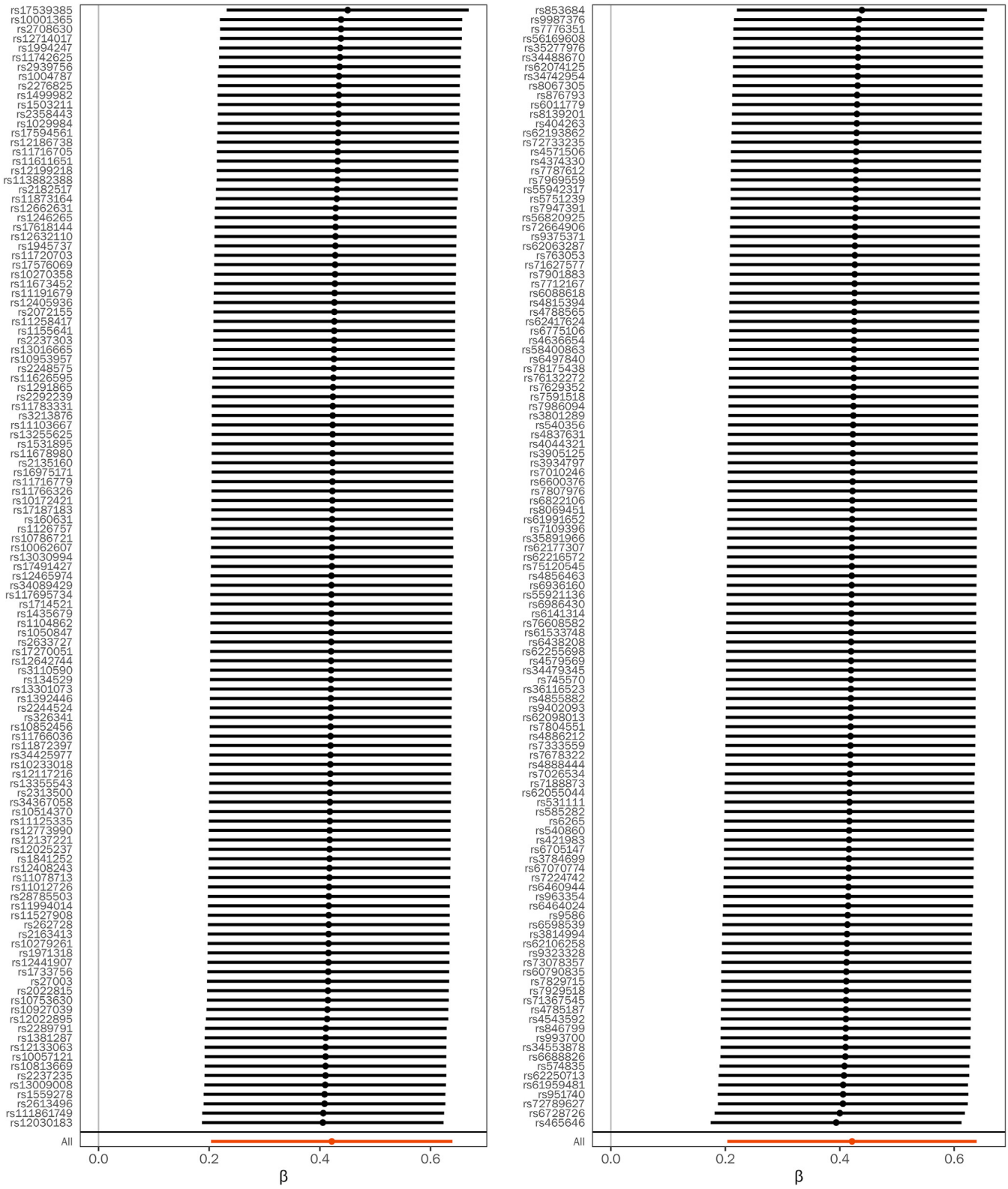

FIG E5. Forest plots showing the results of the leave-one-out analysis. The data have been split across 2 panels to facilitate the visualization of rs ids. The plots show that the beta estimates were not substantially affected by the exclusion of any individual SNP.

TABLE E1. Summary data for the 3 PPP cohorts

Category	UK	HUNT	FinnGen
Clinical presentation			
Age of onset (y), median (IQR)	46 (35-55)	56 (50-65)	53 (42-60)
Concurrent plaque psoriasis, n (%)	82 (28.5)	15 (6.7)	196 (19.5)
Psoriatic arthritis, n (%)	29 (10.1)	56 (24.9)	121 (12.0)
Sex, n (%)			
Female	228 (79.2)	182 (80.9)	718 (71.4)
Male	60 (20.8)	43 (19.1)	288 (28.6)
Smoking status, n (%)			
Current/former smoker	189 (65.7)	151 (67.1)	NA
Never-smoker	20 (6.9)	7 (3.1)	NA
Unknown	79 (27.4)	67 (29.8)	1006 (100)

IQR, Interquartile range; *NA*, not available.

TABLE E2. Results obtained in individual cohorts for genome-wide significant and suggestive association signals

			UK		HUNT		FinnGen		Meta-analysis		
rsID	Position*	EAF/NEAF	*P* value	OR	*P* value	OR	*P* value	OR	*P* value	OR	I^2
rs61802325	1:161,588,097	A/G	1.00×10^{-01}	1.24	1.31×10^{-01}	1.20	9.37×10^{-08}	1.29	1.60×10^{-08}	1.28	0%
rs887467	6:31,141,664	C/G	5.99×10^{-05}	0.70	6.18×10^{-01}	0.92	5.24×10^{-09}	0.77	2.87×10^{-11}	0.75	11.5%
rs73236841	4:37,911,079	A/C	1.11×10^{-01}	0.80	1.30×10^{-03}	0.59	1.25×10^{-03}	0.84	4.79×10^{-06}	0.78	**53%**
rs3798130	5:132,042,146	T/C	2.21×10^{-01}	1.17	3.67×10^{-02}	1.30	8.47×10^{-06}	1.23	6.41×10^{-07}	1.27	0%
rs4075959	5:176,784,612	A/G	3.64×10^{-01}	1.10	3.04×10^{-03}	1.36	4.83×10^{-05}	1.21	1.10×10^{-06}	1.26	3.9%
rs9487605	6:111,582,885	A/G	3.51×10^{-02}	1.23	3.93×10^{-01}	1.10	3.52×10^{-05}	1.21	4.15×10^{-06}	1.23	0%
rs2097442	6:32,422,191	A/G	2.29×10^{-03}	1.22	1.30×10^{-01}	1.24	3.44×10^{-05}	1.22	1.43×10^{-07}	1.29	0%
rs10950151	7:68,306,574	T/C	5.44×10^{-01}	1.17	3.63×10^{-05}	3.66	9.52×10^{-04}	1.33	4.54×10^{-06}	1.54	**80%**
rs1990107	7:84,724,076	T/C	2.58×10^{-01}	1.39	9.42×10^{-03}	2.61	5.21×10^{-06}	1.71	1.75×10^{-07}	2.00	0%
rs11793564	9:111,534,315	A/G	1.42×10^{-01}	1.18	1.49×10^{-02}	1.30	1.47×10^{-04}	1.21	2.87×10^{-06}	1.25	0%
rs4246905	9:117,553,249	T/C	4.98×10^{-02}	0.81	2.29×10^{-02}	0.78	6.47×10^{-05}	0.79	6.16×10^{-07}	0.78	0%
rs9666271	11:85,879,769	T/C	8.76×10^{-02}	1.81	4.51×10^{-01}	1.20	1.27×10^{-05}	1.93	4.58×10^{-06}	1.64	30%
rs860876	12:25,158,319	T/G	2.42×10^{-03}	1.41	2.91×10^{-02}	1.30	2.49×10^{-03}	1.19	4.14×10^{-06}	1.30	0%
rs112872175	17:80,589,958	G/GATAA	5.68×10^{-03}	1.43	1.89×10^{-02}	1.37	6.31×10^{-04}	1.21	1.06×10^{-06}	1.31	0%
rs4817988	21:40,468,838	A/G	9.21×10^{-02}	0.83	5.08×10^{-04}	0.69	1.13×10^{-03}	0.84	2.15×10^{-06}	0.79	28%

Values indicating substantial heterogeneity ($I^2 > 50\%$) are highlighted in bold.
EAF, Effect allele frequency; I^2, percentage of the variability in effect estimates due to heterogeneity rather than sampling error; *NEAF*, non–effect allele frequency; *OR*, odds ratio.
*Coordinates refer to GRCh37.