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A genome-wide meta-analysis of palmoplantar pustulosis implicates T$_H$2 responses and cigarette smoking in disease pathogenesis

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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$_H$2-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$_H$2 responses and cigarette smoking. (J Allergy Clin Immunol 2024;154:657-65.)

Key words: *Palmoplantar pustulosis, genome-wide association study, T$_H$2, cigarette smoking, Mendelian randomization*

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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

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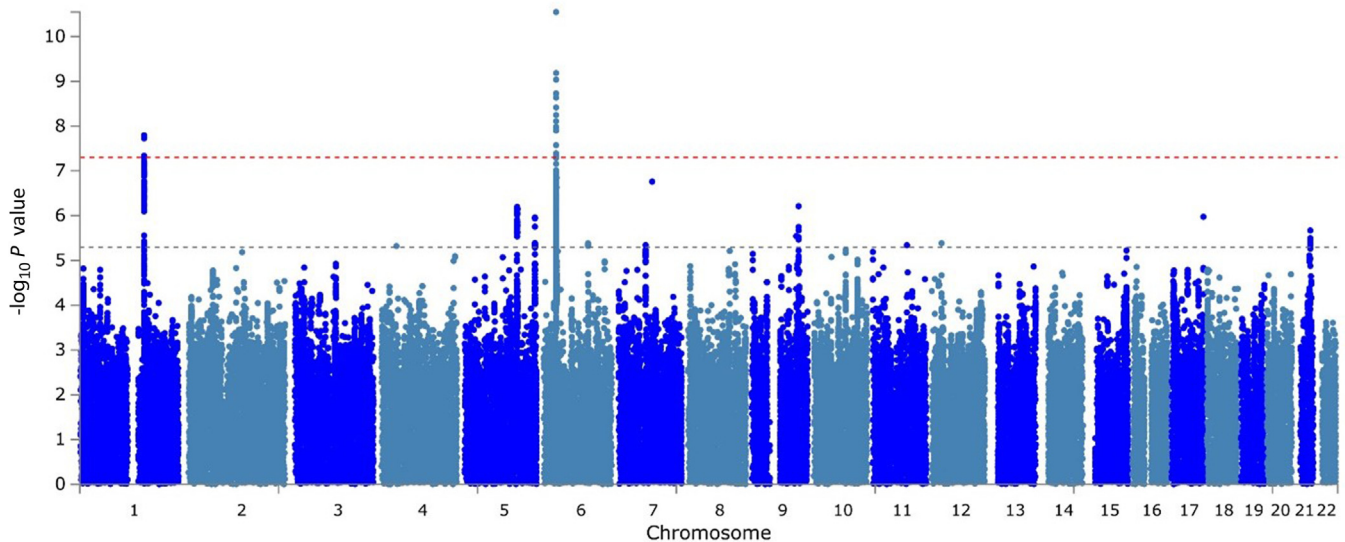
FIG 1. Manhattan plot showing the association signals detected in the GWAS meta-analysis.

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$_H$2-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$_H$2 activation in PPP skin,[8,10] we next examined

4 T$_H$2-mediated disorders (allergic rhinitis, asthma, AD, and UC). We found that PPP shows a positive correlation with AD ($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$_H$2-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.
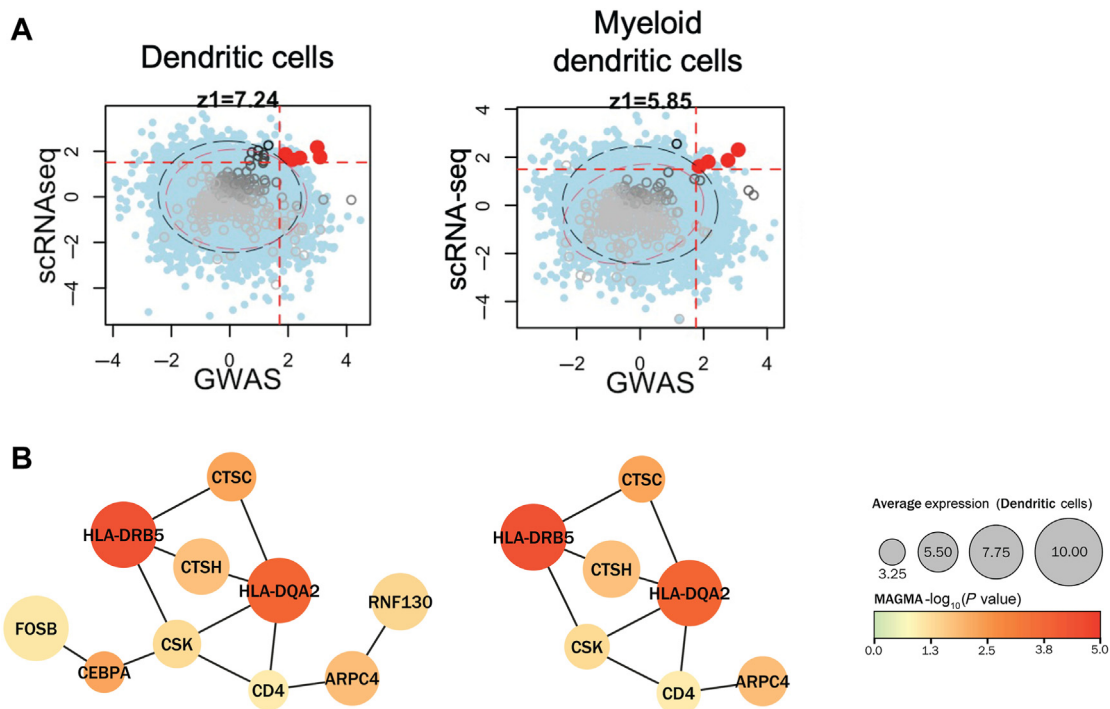
†Nearest gene(s) identified by LocusZoom.

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*.
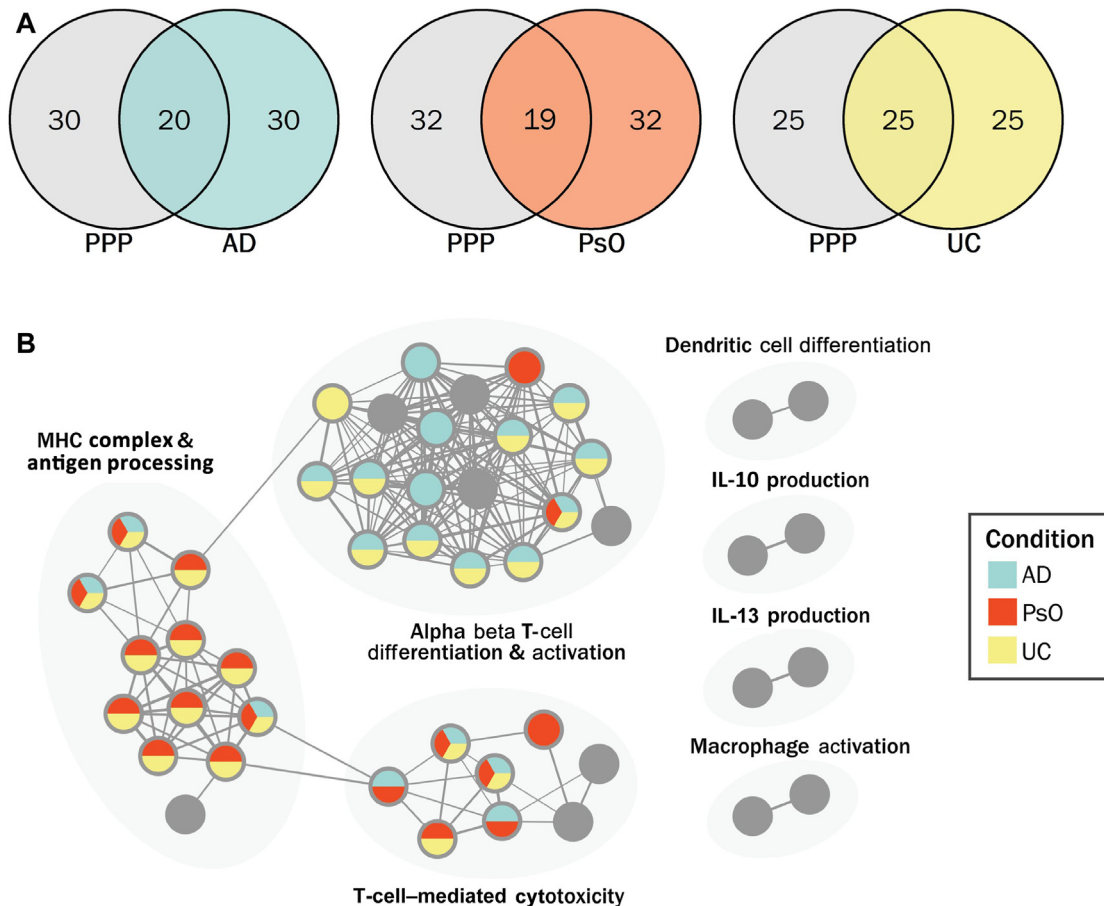
FIG 3. Overlap between GO Biological Process pathways identified from GWAS summary statistics for PPP, plaque psoriasis (PsO), AD, and UC. **A,** Venn diagrams illustrating the overlap between the 50 most significantly enriched pathways identified in each condition. **B,** Cytoscape network analysis 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

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.

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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 Illumina 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.

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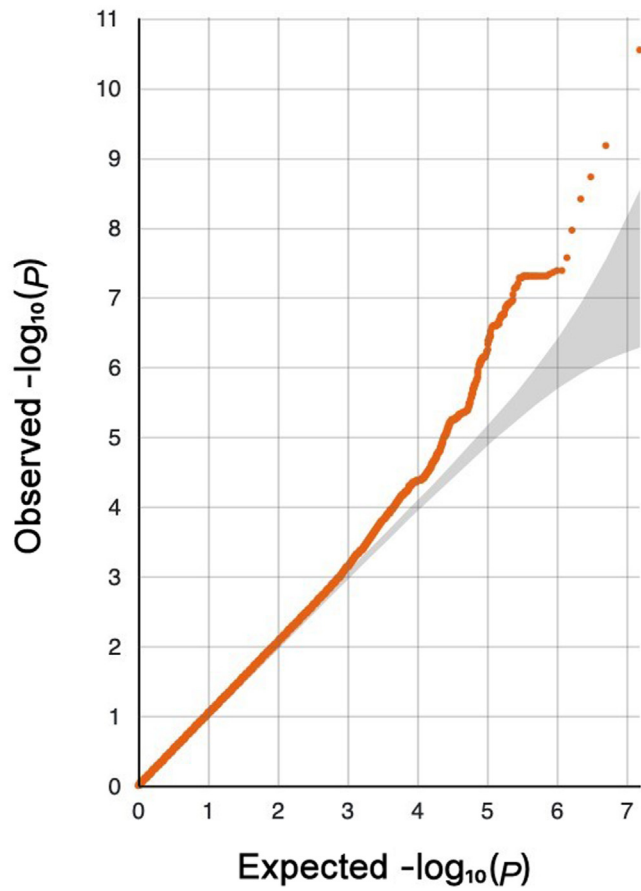
FIG E1. Meta-analysis quantile-quantile plot showing that the distribution of *P* values did not significantly deviate from that expected under the null hypothesis (shaded in gray).
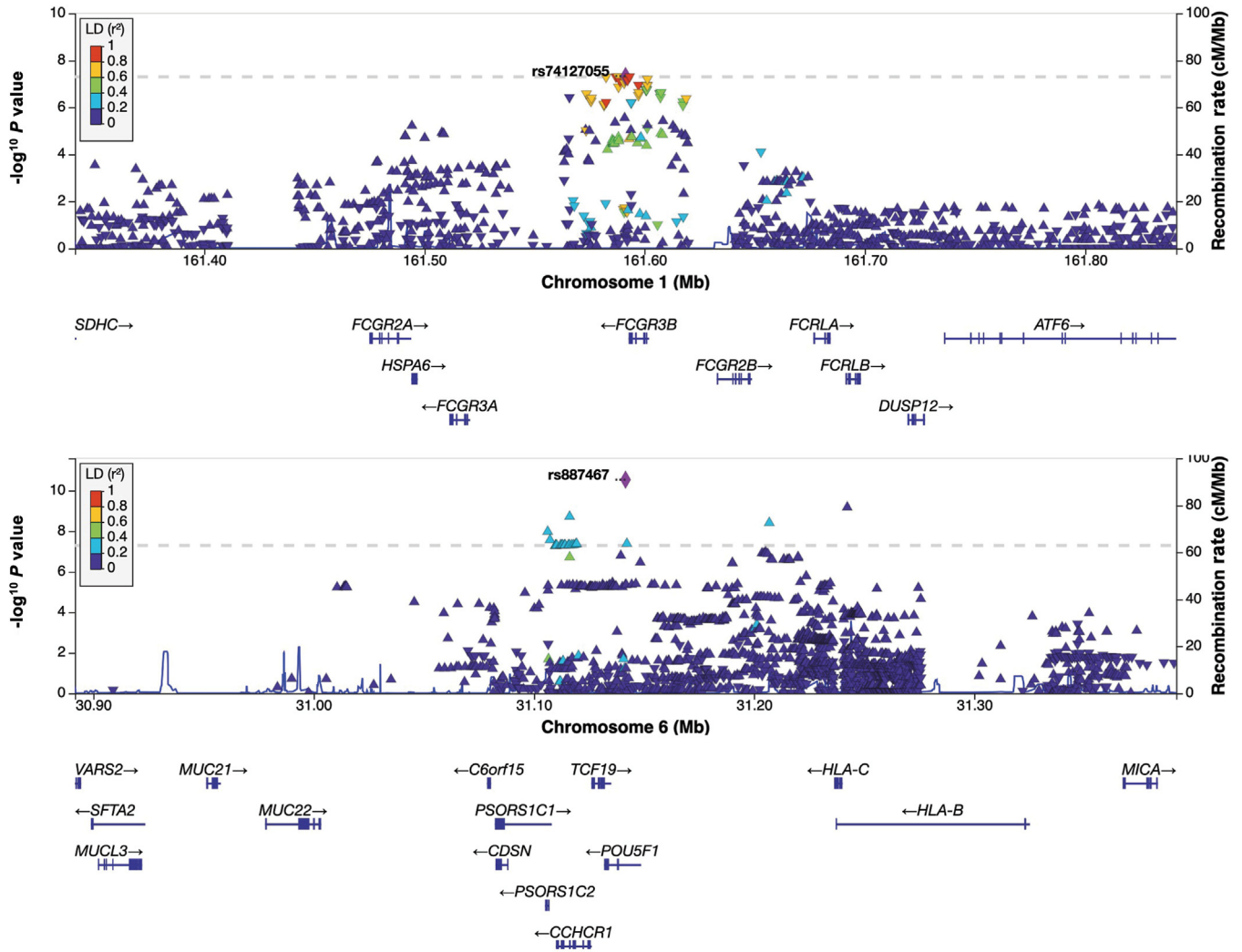
FIG E2. Regional association plots for the 1q23 and 6p21 susceptibility loci. *P* values and recombination rates are plotted against chromosomal coordinates and gene positions.
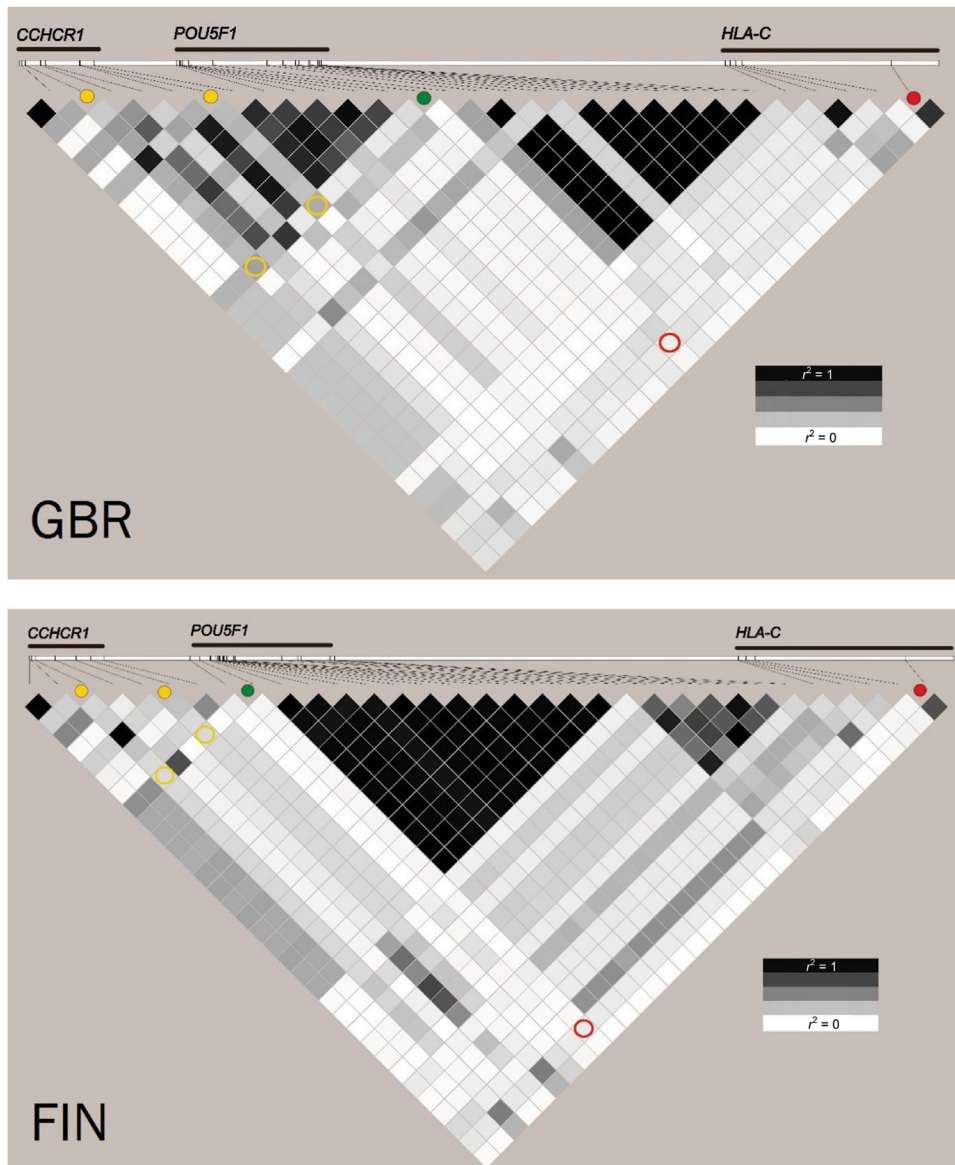
FIG E3. LD conservation plots showing pairwise r^2 between SNPs genotyped by the 1000 Genomes Project in British (GBR) and Finnish (FIN) individuals. The white bar at the top of each plot illustrates the position of the examined SNP with respect to *CCHCR1*, *POU5F1*, and *HLA-C*. The colored circles 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).
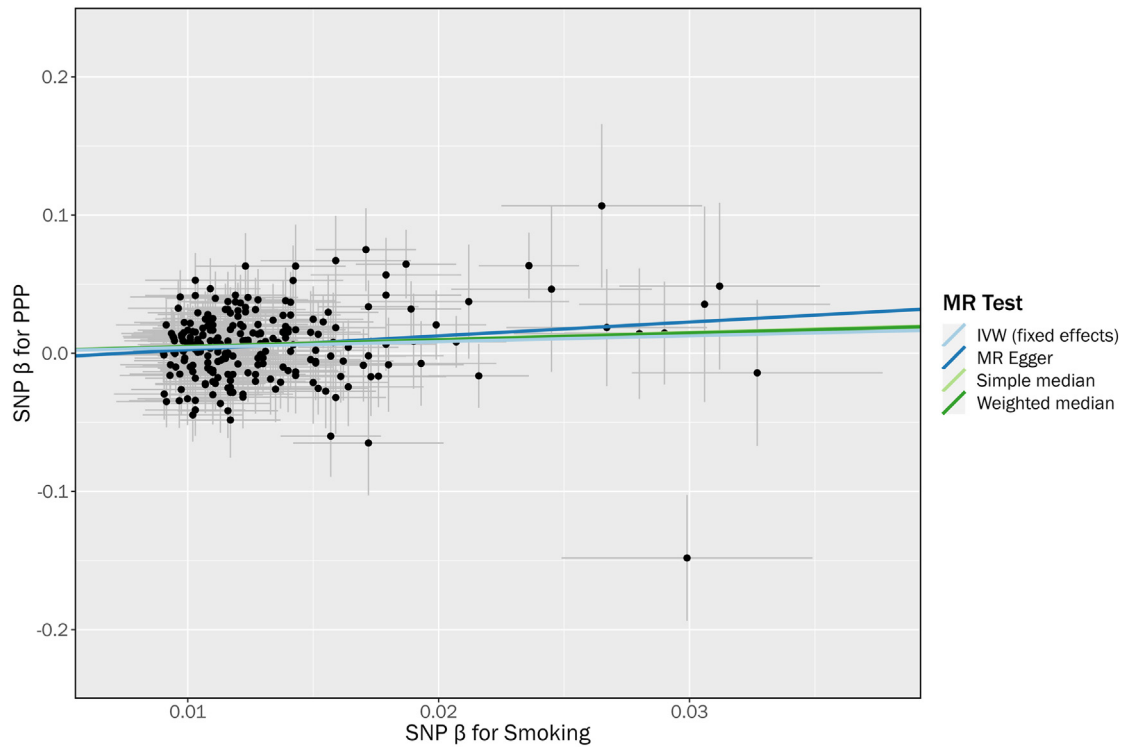
FIG E4. Results of Mendelian randomization. MR scatter plot for the effect of smoking (exposure) on PPP (outcome). A genetically predicted increase in the likelihood of smoking initiation was associated with increased risk of PPP. The slope of each line corresponds to the causal effect estimated with the relevant method.
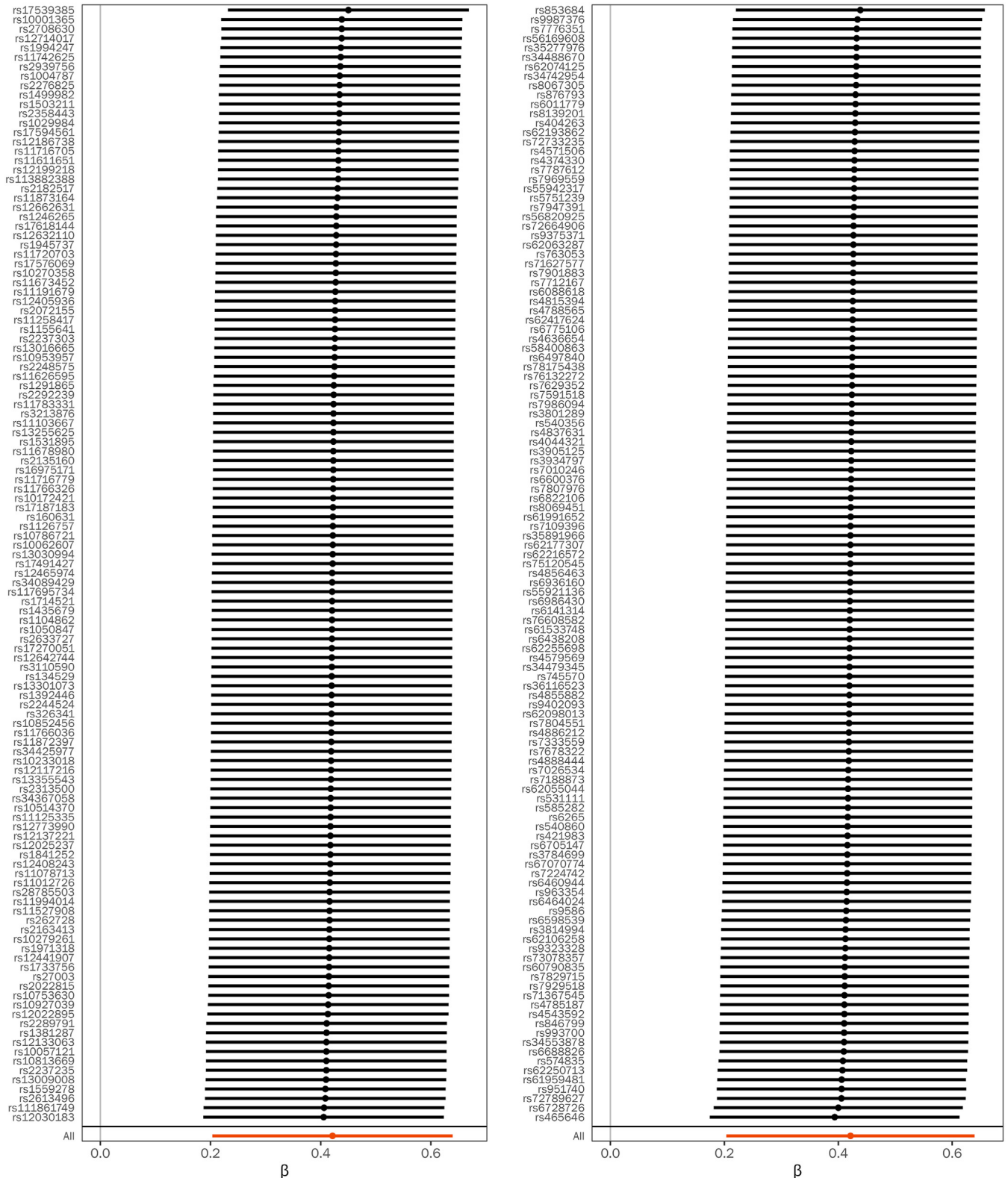
FIG E5. Forest plots showing the results of the leave-one-out analysis. The data have been split across 2 panels to facilitate the visualization of rs ids. The plots show that the beta estimates were not substantially affected by the exclusion of any individual SNP.

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

rsID	Position*	EAF/NEAF	UK P value	UK OR	HUNT P value	HUNT OR	FinnGen P value	FinnGen OR	Meta-analysis P value	Meta-analysis 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.