Genome-wide association study and polygenic risk scores predict psoriasis and its shared phenotypes in Taiwan

JAI-SING YANG[1*], TING-YUAN LIU[2*], HSING-FANG LU[2], SHIH-CHANG TSAI[3], WEN-LING LIAO[4,5], YU-JEN CHIU[6,7], YU-WEN WANG[2] and FUU-JEN TSAI[8-10]

[1]Department of Medical Research, China Medical University Hospital, China Medical University, Taichung 404327, Taiwan, R.O.C.; [2]Million-Person Precision Medicine Initiative, Department of Medical Research, China Medical University Hospital, Taichung 404327, Taiwan, R.O.C.; [3]Department of Biological Science and Technology, China Medical University, Taichung 406040, Taiwan, R.O.C.; [4]Graduate Institute of Integrated Medicine, China Medical University, Taichung 404333, Taiwan, R.O.C.; [5]Center for Personalized Medicine, China Medical University Hospital, Taichung 404327, Taiwan, R.O.C.; [6]Department of Surgery, Division of Plastic and Reconstructive Surgery, Taipei Veterans General Hospital, Taipei 112201, Taiwan, R.O.C.; [7]Department of Surgery, School of Medicine, National Yang Ming Chiao Tung University, Taipei 112304, Taiwan, R.O.C.; [8]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung 404333, Taiwan, R.O.C.; [9]Department of Pediatric Genetics, China Medical University Children's Hospital, Taichung 404327, Taiwan, R.O.C.; [10]Department of Medical Genetics, China Medical University Hospital, Taichung 404327, Taiwan, R.O.C.

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Abstract. Psoriasis is a chronic inflammatory dermatological disease, and there is a lack of understanding of the genetic factors involved in psoriasis in Taiwan. To establish associations between genetic variations and psoriasis, a genome-wide association study was performed in a cohort of 2,248 individuals with psoriasis and 67,440 individuals without psoriasis. Using the ingenuity pathway analysis software, biological networks were constructed. Human leukocyte antigen (HLA) diplotypes and haplotypes were analyzed using Attribute Bagging (HIBAG)-R software and chi-square analysis. The present study aimed to assess the potential risks associated with psoriasis using a polygenic risk score (PRS) analysis. The genetic association between single nucleotide polymorphisms (SNPs) in psoriasis and various human diseases was assessed by phenome-wide association study. METAL software was used to analyze datasets from China Medical University Hospital (CMUH) and BioBank Japan (BBJ). The results of the present study revealed 8,585 SNPs with a significance threshold of $P<5x10^{-8}$, located within 153 genes strongly associated with the psoriasis phenotype, particularly on chromosomes 5 and 6. This specific genomic region has been identified by analyzing the biological networks associated with numerous pathways, including immune responses and inflammatory signaling. HLA genotype analysis indicated a strong association between *HLA-A*02:07* and *HLA-C*06:02* in a Taiwanese population. Based on our PRS analysis, the risk of psoriasis associated with the SNPs identified in the present study was quantified. These SNPs are associated with various dermatological, circulatory, endocrine, metabolic, musculoskeletal, hematopoietic and infectious diseases. The meta-analysis results indicated successful replication of a study conducted on psoriasis in the BBJ. Several genetic loci are significantly associated with susceptibility to psoriasis in Taiwanese individuals. The present study contributes to our understanding of the genetic determinants that play a role in susceptibility to psoriasis. Furthermore, it provides valuable insights into the underlying etiology of psoriasis in the Taiwanese community.

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease (1). According to a study by the World Health Organization, it is a significant global health concern, affecting 125 million individuals worldwide (2). According to epidemiological studies, the global prevalence of psoriasis ranges from 1.0-11.4% (3). Specifically, the prevalence of psoriasis is 0.24% in Taiwan, as reported by the National Health Insurance Research Database for Taiwan (4); 0.340% in Japan (5); 0.453% in South Korea (6); and 0.470% in China (7). Psoriasis, a common dermatological condition, is characterized by persistent inflammation affecting several systems in addition to the skin (8). Psoriasis often causes significant psychological distress, which reduces the overall quality of

Correspondence to: Dr Fuu-Jen Tsai, Department of Medical Genetics, China Medical University Hospital, 2 Yude Road, Taichung 404327, Taiwan, R.O.C.
E-mail: 000704@tool.caaumed.org.tw

*Contributed equally

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life (9). Symptoms of psoriasis include distinct erythematous plaques on the skin, accompanied by silvery scales covering the affected areas, often accompanied by itching and pain (10). Clinical manifestations of psoriasis include subtypes such as plaque, guttate, nail, pustular, scalp and palmoplantar psoriasis (11,12). The etiology of psoriasis encompasses various elements, including genetic predispositions, environmental influences, immunologic responses (both innate and adaptive), lifestyle factors such as stress, bacterial or viral infections, and therapeutic interventions (3,4).

A characteristic feature of psoriasis is the hyper-proliferation of keratinocytes, fibroblasts, and endothelial cells, triggering immune system activation, inflammatory response and new blood vessel formation (neovascularization or angiogenesis) (10,13). Genetic predispositions and environmental influences are significant factors that trigger these effects (3,11). Genetic studies reveal that >10% of patients with psoriasis have a familial connection (14-16). Numerous genome-wide association studies (GWAS) conducted across various nations have identified >100 susceptibility loci associated with psoriasis, including human leukocyte antigen *(HLA)-Cw6*, tyrosine kinase 2 (*TK2*), interleukin-12B (*IL-12B*), interleukin-23 receptor (*IL-23R*) and late Cornified Envelope 3B/C (*LCE3B/3C*) (17-20). However, in Taiwan, no definitive genetic susceptibility loci or associated processes have been identified.

In clinical research, the polygenic risk score (PRS) is used as an analytical tool (21). Furthermore, the increase in sample size for GWAS has enhanced the power and effectiveness of the PRS. Therefore, a PRS based on GWAS is essential for personalized medicine (22). The PRS provides an accurate and efficient means of predicting the health status and susceptibility of an individual to disease (23). In addition to evaluating the genetic composition of an individual, PRS can provide valuable information regarding the efficacy of therapy and the likelihood of positive or negative outcomes, even before symptoms are evident (21,24). Furthermore, PRS provides an opportunity for early detection of abnormal test results before they occur (25,26). Through this approach, healthcare practitioners can prescribe preventive measures that are customized to the genetic profile of each patient (23,27,28).

In the present study, GWAS, PRS and phenome-wide association study (PheWAS) were conducted on gene variations in patients with psoriasis using the Taiwanese gene database of China Medical University Hospital (CMUH). A meta-analysis of single nucleotide polymorphism (SNP) sites associated with psoriasis in datasets from CMUH and BioBank Japan (BBJ) was also conducted (29). Notably, the genetic diversity among individuals from Taiwan is significantly different from that in other racial groups.

Materials and methods

Study design, sample sources and characteristics. The electronic medical records of the CMUH were analyzed for clinical data of patients with psoriasis between 2003 and 2020. All the included patients were validated by physicians with specific expertise in the field of psoriasis. The present study used the following International Classification of Diseases (ICD) diagnostic clinical modification (CM) codes: L40.0, L40.1, L40.4, L40.50, L40.8, L40.9, L41.3, L41.4, L41.5, L41.8 and L41.9; and the following ICD-9-CM codes: 696.1, 696.10, 696.2 and 696.8 (30). The number between ICD and CM indicates the version of ICD. Currently, the clinical practice of Taiwan includes two versions of ICD CM, versions 9 and 10. These two versions (ICD-9-CM and ICD-10-CM) have different codes, and therefore, their specifications are required. In Taiwan, clinicians mostly continue to record diagnoses using ICD-9 codes, which are then converted to ICD-10 codes through backend programs. This practice aligns with government regulations that mandated a complete transition to ICD-10 use for reporting purposes after 2015 (31). Regarding psoriasis diagnosis, there are no significant differences between ICD-9 and ICD-10. However, there is a primary difference in the coding for psoriasis between the two versions in terms of the level of detail and specificity. Under ICD-9, psoriasis was primarily coded as 696.1 for psoriatic arthropathy and 696.0 for other types of psoriasis without specifying the type of psoriasis. On the other hand, the ICD-10 offers a more detailed classification of psoriasis, allowing healthcare professionals to accurately specify the type and site of psoriasis. This increased specificity in ICD-10 enables improved tracking of the prevalence and treatment outcomes of various types of psoriasis, which in turn facilitates more accurate public health surveillance and research on psoriasis treatment and its effectiveness (32,33).

A schematic representation of the study design used to investigate psoriasis is shown in Fig. 1. The Precision Medicine Project was approved by the ethics committee of the institutional review board (approval nos. CMUH110-REC3-005 and CMUH111-REC1-176) and was approved by the Institutional Review Board of China Medical University Hospital (Taichung, Taiwan). Patient data, including genetic information (genetic variations detected by the TPMv1 SNP array), laboratory tests [C-reactive protein and erythrocyte sedimentation rate (ESR)], diagnoses, age and sex, were compiled for subsequent statistical analysis. The inclusion criteria were as follows: i) Patients with the ICD-9 and ICD-10 diagnostic codes for psoriasis; and ii) patients diagnosed with psoriasis at least three times at China Medical University Hospital. Examples of excluded autoimmune skin diseases include lupus erythematosus, dermatomyositis, systemic sclerosis (scleroderma), vitiligo and alopecia areata.

The boxes on either side of the flow arrows in Fig. 1 represent exclusion criteria. In the analysis workflow, quality control (QC) was performed according the following steps using PLINK (https://www.cog-genomics.org/plink/; V.1.90). First, variations were checked for and those with a missing rate >10% (-geno 0.1) were eliminated. Next, the individuals were checked and those with a missing rate >10% (-mind 0.1) were removed. Next, adherence to the Hardy-Weinberg equilibrium by PLINK (https://www.cog-genomics.org/plink/; V.1.90) was verified for each variation, and variations that failed the hypothesis test with $P>1x10^{-6}$ (-hwe $1x10^{-6}$) were removed (34,35). The occurrence rate for each variation was also calculated, which required a minor allele frequency of 1 in 10,000 (-maf $1x10^{-4}$). Additionally, the heterozygosity for each sample was examined and individuals with heterozygosity exceeding three times the interquartile range were excluded. Principal component analysis on each individual

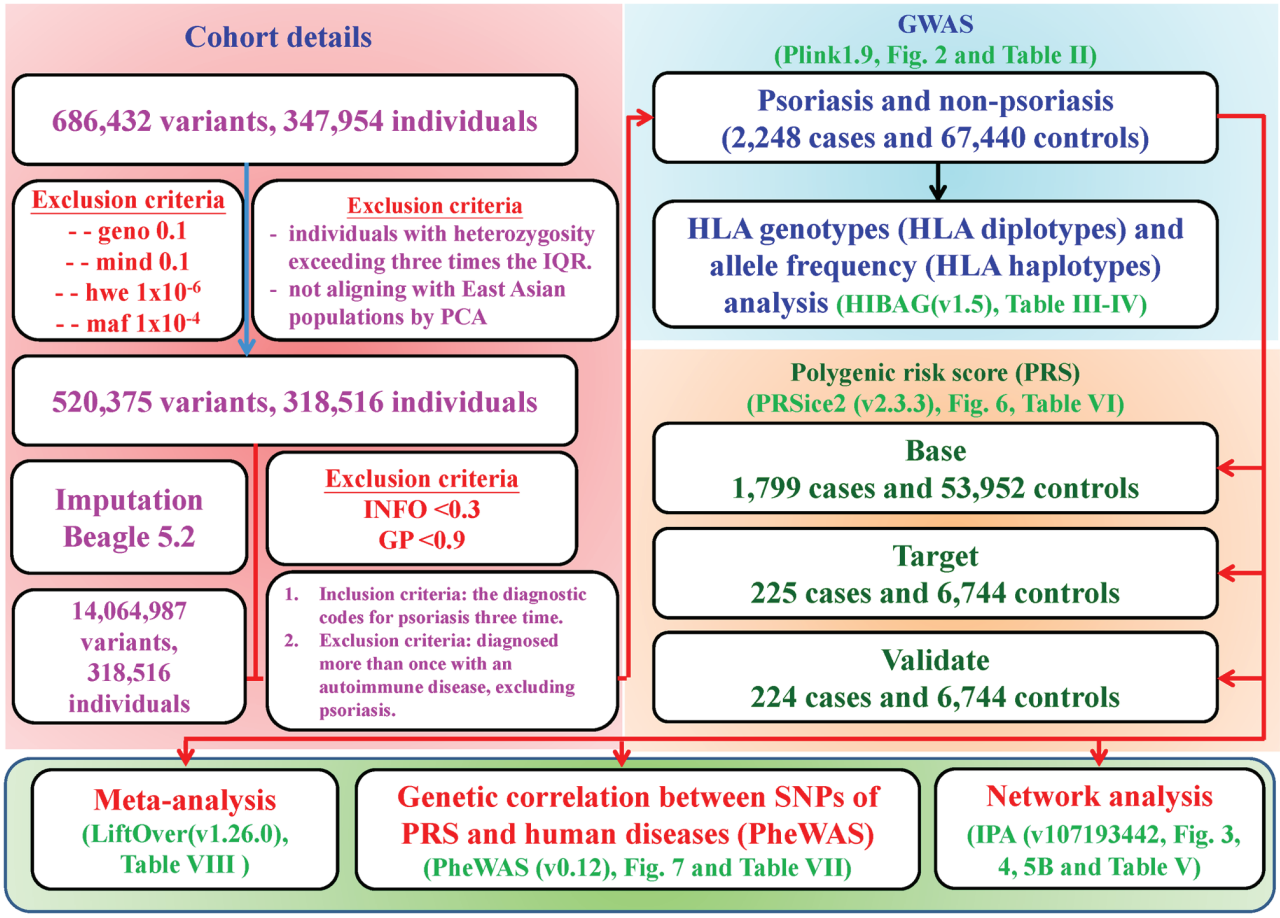


Figure 1. Flowchart of the experimental design on psoriasis. After the quality control of genetic markers and samples, dense genotype data were obtained through imputation. For GWAS and HLA sub-types analyses, the individuals were stratified into two groups, psoriasis and non-psoriasis. For the PRS analysis, the cohort was further divided into three groups: Base, target and validation groups (8:1:1). Finally, the bioinformatics network analysis and association between SNPs and human diseases were analyzed by IPA software. A meta-analysis of psoriasis was performed on the CMUH and BBJ. GWAS, genome-wide association study; HLA, human leukocyte antigen; PRS, polygenic risk score; SNP, single nucleotide polymorphism; IPA, Ingenuity Pathway Analysis; CMUH, China Medical University Hospital; BBJ, BioBank Japan; IQR, interquartile range; PCA, principal component analysis; INFO, imputation quality score; GP, genomic prediction; PheWAS, phenome-wide association.

was performed and those who did not align with the East Asian populations from the 1,000 Genomes Project were excluded (36). After imputation, variations with an information score of <0.3 were removed to ensure accuracy. Variations with genotype probabilities <0.9 were also eliminated to guarantee reliability (37). GWAS and HLA subtype analyses were conducted on 2,248 patients with psoriasis and 67,440 controls (Fig. 1; right). The TPMv1 customized SNP array was obtained from Thermo Fisher Scientific, Inc., according to the manufacturer's instructions (38).

The association between the SNP array and psoriasis was investigated using PLINK (V.1.90). A Manhattan plot and quantile-quantile plot (QQ) (https://cran.r-project.org/web/packages/qqman/index.html; version 0.1.9) was generated using the R programming language (https://cran.r-project.org/; version: R 4.1.0) within the R Studio (https://posit.co/downloads/; version: R 1.4.1717) integrated development environment (38,39). Table SI presents the GWAS analysis results. The Gene Symbol and Entrez Gene Name in the last two columns are the information obtained after inputting into the Ingenuity Pathway Analysis (IPA) software and then merged into Table SI.

Study limitations. In Taiwan, under the regulations of the National Health Insurance, billing can be conducted solely with ICD codes, which do not categorize the severity of conditions (40). This applies to both the ICD-9 and ICD-10. In the present study, only ICD diagnosis codes were used for categorization, with diagnostic data spanning 19 years and being recorded by numerous physicians. Therefore, distinguishing severity levels among participants is challenging. Upon consultation with professional physicians, it was determined that only a minority would document severity levels in an unstructured manner for research purposes, further complicating the analysis owing to the unstructured nature of the data. Therefore, this limitation was added to the manuscript.

Biological networks analysis. GWAS was employed to analyze biological networks across the genome, with a significance threshold of $P<5x10^{-8}$ (PLINK; V.1.90). This analysis led to the identification of a comprehensive set of 8,585 SNPs associated with psoriasis. A molecular network was constructed using core analysis in the IPA software (https://digitalinsights.qiagen.com/product-login/; version: 107193442; Qiagen Sciences, Inc.). The statistical significance of the available networks was

Table I. Selected characteristics of the study population.

Variables	Cases (n=2,248)	Controls (n=67,440)	P-value
Age, mean (SD)	45.75 (±16.801)	45.75 (±16.798)	>0.999
Sex, n (%)			>0.999
Male	1,131 (59.2)	39,930 (59.2)	
Female	917 (40.8)	27,510 (40.8)	
Lifestyle habits, n (%)			
Smoking			0.853
Yes	37 (15.2)	5,727 (15.8)	
No	207 (84.2)	30,424 (84.2)	
Not available	2,004	31,289	
Drinking			0.245
Yes	24 (9.8)	4,506 (12.5)	
No	220 (90.2)	31,645 (87.5)	
Not available	2,004	31,289	
Betel nut			>0.999
Yes	14 (5.7)	2,090 (5.8)	
No	230 (94.3)	34,061 (94.2)	
Not available	2,004	31,289	
Inflammation-related test values			
CRP (mean, ±SD, n)	2.76, ±4.83, 74	3.83, ±6.16, 643	0.148
ESR (mean, ±SD, n)			
Male	26.26, ±29.00, 821	24.85, ±31.24, 5,786	0.223
Female	31.92, ±28.70, 594	24.28, ±26.04, 3,927	$5.34x10^{-11}$

P<0.05 level. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

assessed using Fisher's exact test with a significance level of P<0.05 (39,41,42).

Imputation and prediction of HLA genotypes. The HLA genotypes for each participant in the study were computed using HLA genotype imputation via attribute tagging (HIBAG-R) (https://bioconductor.org/packages/release/bioc/html/HIBAG.html; V1.5). HIBAG allowed for the determination of haplotypes and diplotypes for individuals, while maintaining P>0.90. Chi-square analysis was conducted to examine the HLA haplotypes and diplotypes to investigate the association between these genetic factors and the incidence of psoriasis. Bonferroni correction was applied to address multiple testing (39,43).

PRS analysis. To calculate the PRS, the CMUH cohort was divided into three distinct datasets including base, target and validation (8:1:1 ratio). PRS analysis was performed on 1,799 psoriasis patients and 53,952 controls in the base group, 225 psoriasis patients and 6,744 controls in the target group, and 224 psoriasis patients and 6,744 controls in validation group. A primary dataset was used to investigate the association between the variables under study and psoriasis using PLINK1.9. The PRS was calculated based on the target dataset and the PRSice2 (https://choishingwan.github.io/PRSice/; v2.3.3) tool while excluding variants with a missing rate of >1% and those deviating from the Hardy-Weinberg equilibrium with P<0.001. The present study utilized reference data from the 1,000 Genomes Phase 3 for the East Asian population (https://www.internationalgenome.org/data; v5b.20130502). The PRS was calculated by normalizing the z-scores. The PRS, clinical data, or a combination of both was used to construct logistic regression models. The models were subsequently adjusted for sex, age, *HLA-A*02:07* and *HLA-C*06:02* (22).

PheWAS. A genetic association between SNPs from PRS and diseases was constructed through logistic regression models, using the 'PheWAS' package (https://github.com/PheWAS/PheWAS; v0.12) in R programming language within the R Studio integrated development environment (https://cran.r-project.org/; R 4.1.0). PheWAS results were defined using the phecode schema with ICD diagnostic codes (10,750 unique ICD-10 codes and 3113 ICD-9 codes). Statistical significance of the available networks was assessed using Fisher's exact test with a significance level of P<5E-05 (44).

Meta-analysis of SNP loci on psoriasis. GWAS summary statistics for psoriasis were obtained from the BBJ (29). The summary statistics of psoriasis were downloaded from BBJ (https://pheweb.jp/downloads), and using the LiftOver method (https://hgdownload.soe.ucsc.edu/goldenPath/hs1/liftOver/; v1.26.0), the position of the BBJ genome construction gene, hg19, was transferred to GRCh38. In total 13,433,353 variations remained in the BBJ dataset. The meta-analysis

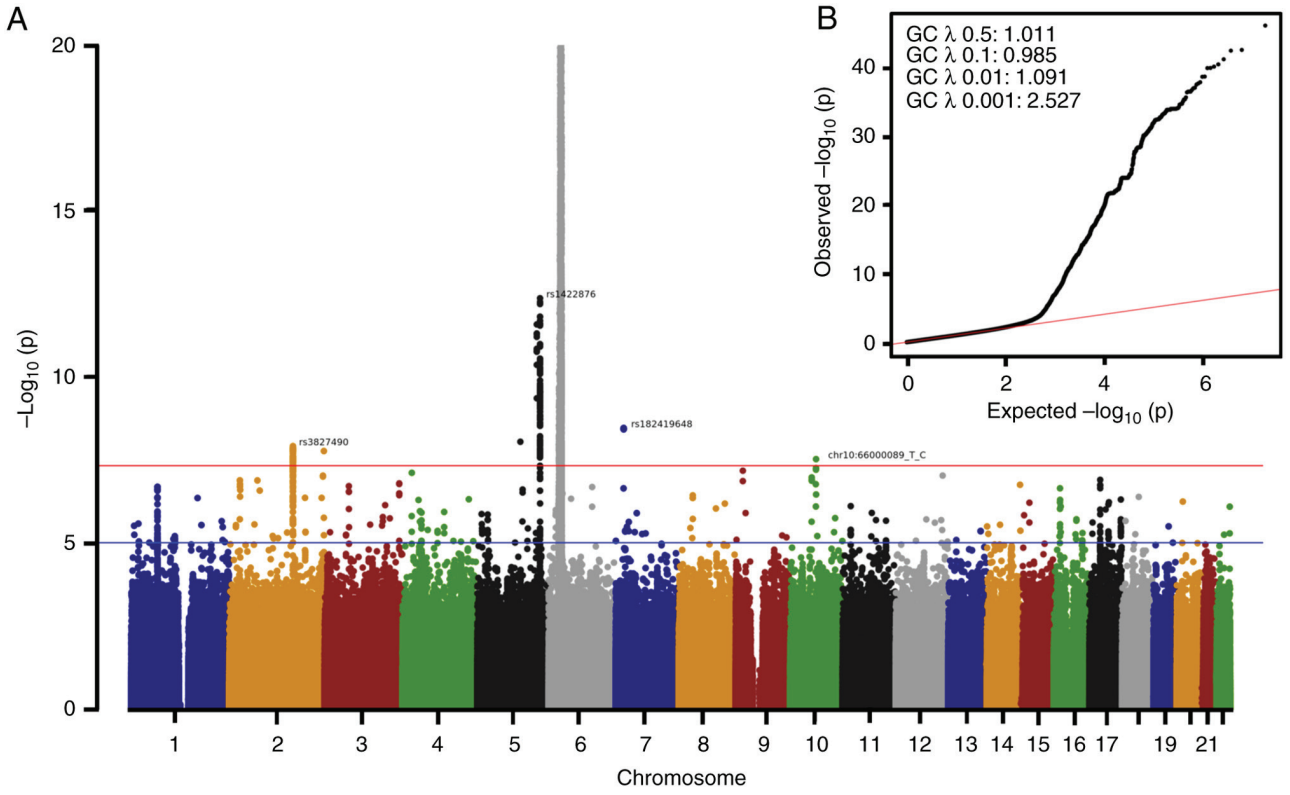


Figure 2. Manhattan plots and quantile-quantile plots of genome-wide association studies for psoriasis. (A) Manhattan plot analysis for the association between genome-wide variations with psoriasis. SNPs that passed quality control are plotted on the x-axis, according to their chromosomal locations vs. the y-axis in the Manhattan plot analysis (-log10 P-value). The red line represents $P=5x10^{-8}$, and the blue line represents $P=1x10^{-5}$. (B) Quantile-Quantile plot analysis of the association of genome-wide variations with psoriasis (λ=1.011; based on median Chi-square). The red line in a QQ plot represents the reference line where expected values and observed values are the same. SNP, single nucleotide polymorphism; GC, group-specific component.

was conducted using METAL software (https://genome.sph.umich.edu/wiki/METAL_Documentation; version, generic-metal-2011-03-25) (45).

Statistical analysis. Baseline continuous and categorical variables were examined using statistical tests such as the unpaired Student's t-test, χ^2 test and Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS (https://www.ibm.com/spss; version 22) and R (version R 4.1.0) software (46).

Results

Taiwanese GWAS of psoriasis. The present study presents the results of a GWAS involving 67,440 controls and 2,248 cases. The control group included 39,930 men (59.2%) and 27,510 women (40.8%), with a mean age of 45.75±16.798 years. The psoriasis cohort included 1,331 men (59.2%) and 917 women (40.8%), with a mean age of 45.75±16.801 years. The distribution of age and sex did not differ significantly between the groups (Table I). Habit-related clinical features such as smoking, alcohol consumption and betel consumption were not statistically significant. However, the comparison of ESR values between female patients with psoriasis and those in the control group revealed a statistically significant difference ($P<5.34x10^{-11}$). The Manhattan (Fig. 2A) and QQ (Fig. 2B) plots are useful tools for visualizing GWAS results. The Manhattan plots (Fig. 2A) demonstrated the strongest associations between all the SNPs on a genomic scale. Notably, psoriasis was associated with 8,585 SNPs at a specific position: 14,064,987 (Table SI; $P<5x10^{-8}$). As shown in Table II, SNP-induced amino acid mutations were significantly associated with psoriasis ($P<5x10^{-8}$). Missense mutations were found in a variety of genes; furthermore, the rs34182778 variant was characterized by a DNA insertion within the corneodesmosin (*CDSN*) gene, whereas the rs200838925 variant was characterized by a DNA deletion within the mucin 22 (*MUC22*). The aforementioned findings suggested that these loci and gene mutations may share a common function, pathway or relevance to psoriasis. In the present study, the following 92 novel genomic markers for psoriasis were identified through GWAS and PRS (Table SI). Additionally, 61 previously reported genomic markers associated with psoriasis in Taiwanese populations were identified (Table SI): ATP binding cassette subfamily F member 1 (47), advanced glycosylation end-product specific receptor (*AGER*) (48), allograft inflammatory factor 1 (49), Annexin A6 (50), butyrophilin-like 2 (*BTNL2*) (51), complement C2 (52), chromosome 6 open reading frame 15 (53,54), complement factor B (52,55), fibroblast activation protein α (56), HLA complex group 26 (57), HLA complex group 27 (57), HLA complex group 9 (58), HLA complex P5 (59,60), HLA complex P5B (59,60), major histocompatibility complex, class I, A (*HLA-A*) (61), major histocompatibility complex, class I, B (*HLA-B*) (62,63), major histocompatibility complex, class I, C (*HLA-C*) (53,54), major histocompatibility complex,

Table II. SNP loci associated with amino acid variation site of GWAS in psoriasis ($P<5x10^{-8}$).

Chr.	ID	P-value	Gene symbol	DNA consequence	Amino acid position	Amino acid variation	SNP loci and psoriasis association	Gene and psoriasis association	(Refs.)
6	rs130076	$4.05x10^{-34}$	*CCHCR1*	Missense	103, 109	R/W	Reported	Reported	(165)
6	rs9366785	$8.28x10^{-21}$	*PRRC2A*	Missense	1,884	G/S	Novel	-	-
6	rs41257954	$2.68x10^{-30}$	*POU5F1*	Missense	30	V/F	Novel	Reported	(166,167)
6	rs12722477	$6.29x10^{-19}$	*HLA-G*	Missense	134	L/I	Novel	Reported	(113)
6	rs12211410	$2.75x10^{-18}$	*TNXB*	Missense	1,255	R/P	Novel	Reported	(168)
6	rs1130363	$4.95x10^{-18}$	*HLA-G*	Missense	333	R/S	Novel	Reported	(113)
6	rs118062293	$1.12x10^{-17}$	*LY6G6D*	Missense	112	R/C	Novel	-	-
6	rs3132580	$1.49x10^{-17}$	*MUCL3*	Missense	1,295	E/K	Novel	-	-
6	rs17207867	$1.58x10^{-17}$	*DXO*	Missense	261	H/Q	Novel	-	-
6	rs3096696	$4.19x10^{-17}$	*PPT2*	Missense	34	A/E	Novel	-	-
6	rs3096697	$8.26x10^{-17}$	*EGFL8*	Missense	86	R/K	Novel	-	-
6	rs2227956	$3.24x10^{-16}$	*HSPA1L*	Missense	493	T/M	Novel	Reported	(71)
6	rs28732176	$3.48x10^{-16}$	*FKBPL*	Missense	90	A/T	Novel	-	-
6	rs2280801	$5.22x10^{-16}$	*PRRC2A*	Missense	106	P/Q	Novel	-	-
6	rs1049622	$7.49x10^{-16}$	*DDR1*	Missense	175	S/R	Novel	-	-
6	rs2233984	$1.03x10^{-15}$	*C6orf15*	Missense	291	G/V	Novel	Reported	(53)
6	rs2074504	$1.02x10^{-13}$	*PRR3*	Missense	159	H/Q	Novel	-	-
6	rs2074466	$3.39x10^{-13}$	*OR10C1*	Missense	174	P/Q	Novel	-	-
6	rs61730668	$3.84x10^{-13}$	*MAS1L*	Missense	72	A/V	Novel	-	-
6	rs9263726	$5.47x10^{-13}$	*PSORS1C1*	Missense	37	R/H	Reported	Reported	(154)
6	rs3134900	$5.89x10^{-13}$	*MICB*	Missense	121	I/M	Novel	Reported	(76)
6	rs2074469	$7.35x10^{-13}$	*OR10C1*	Missense	60	F/L	Novel	-	-
6	rs9394078	$8.47x10^{-13}$	*ZBTB12*	Missense	49	V/L	Novel	-	-
6	rs1576	$1.61x10^{-12}$	*CCHCR1*	Missense	776	S/F	Reported	Reported	(169)
6	rs375368228	$2.14x10^{-12}$	*CDSN*	Missense	509	L/P	Novel	Reported	(146)
6	rs2233953	$4.50x10^{-12}$	*PSORS1C2*	Missense	84	P/S	Novel	Reported	(53)
6	rs187982887	$5.36x10^{-12}$	*DDR1*	Missense	670	F/L	Novel	-	-
6	rs1052486	$6.71x10^{-12}$	*BAG6*	Missense	619	S/A	Novel	-	-
6	rs72502536	$8.62x10^{-12}$	*MUC22*	Missense	171	I/V	Novel	Reported	(78)
6	rs3734814	$1.37x10^{-11}$	*HLA-F*	Missense	353	N/H	Novel	Reported	(69)
6	rs130066	$1.49x10^{-11}$	*CCHCR1*	Missense	164	S/R	Reported	Reported	(165)
6	rs3734815	$1.55x10^{-11}$	*HLA-F*	Missense	353	N/I	Novel	Reported	(114)
6	rs1046089	$1.90x10^{-11}$	*PRRC2A*	Missense	1,740	R/H	Novel	-	-
6	rs34182778	$2.02x10^{-11}$	*CDSN*	Insertions	149-150	GS/G	Novel	-	-
6	rs144128934	$2.78x10^{-11}$	*ZKSCAN4*	Missense	88	S/T	Novel	-	-
6	rs3131787	$2.85x10^{-11}$	*SFTA2*	Missense	37	N/S	Novel	-	-
6	rs9380254	$5.96x10^{-11}$	*MICA*	Missense	16	R/H	Novel	Reported	(75)
6	rs2294746	$8.20x10^{-11}$	*OR2I1P*	Missense	227	C/W	Novel	-	-
6	rs707926	$2.52x10^{-10}$	*VARS1*	Missense	875	D/E	Novel	-	-
6	rs1059510	$3.17x10^{-10}$	*HLA-E*	Missense	98	N/K	Novel	Reported	(68,115)
6	rs204883	$3.21x10^{-10}$	*TNXB*	Missense	2,232	D/E	Novel	Reported	(168)
6	rs12722482	$4.15x10^{-10}$	*HLA-G*	Missense	282	T/K	Novel	Reported	(113,170)
6	rs3130453	$4.44x10^{-10}$	*CCHCR1*	Missense	78	W/C	Reported	Reported	(171)
6	rs143175221	$8.81x10^{-10}$	*HFE*	Missense	295	V/A	Novel	-	-
6	rs11965542	$1.75x10^{-9}$	*ZSCAN26*	Missense	83	E/K	Novel	-	-
6	rs149494377	$3.08x10^{-9}$	*H2AC15*	Missense	48	A/G	Novel	-	-
6	rs61978565	$3.16x10^{-9}$	*OR11A1*	Missense	80	M/T	Novel	-	-
6	rs76142796	$3.17x10^{-9}$	*OR12D1*	Missense	111	M/T	Novel	-	-
6	rs79293918	$4.25x10^{-9}$	*OR2J3*	Missense	240	V/A	Novel	-	-
6	rs9267799	$4.64x10^{-9}$	*TNXB*	Missense	1,414	R/Q	Novel	Reported	(168)

Table II. Continued.

Chr.	ID	P-value	Gene symbol	DNA consequence	Amino acid position	Amino acid variation	SNP loci and psoriasis association	Gene and psoriasis association	(Refs.)
6	rs61732185	$5.64x10^{-9}$	*OR2H1*	Missense	63	D/N	Novel	-	-
6	rs117708355	$5.78x10^{-9}$	*MDC1*	Missense	533	S/L	Novel	-	-
6	rs1150723	$7.34x10^{-9}$	*PGBD1*	Missense	42	I/M	Novel	-	-
6	rs76463649	$8.43x10^{-9}$	*ZSCAN26*	Missense	15	N/S	Novel	-	-
6	rs9267795	$9.40x10^{-9}$	*TNXB*	Missense	3,214	G/V	Novel	Reported	(168)
6	rs200838925	$9.71x10^{-9}$	*MUC22*	Deletion	983-1,005	ETTTASTEGS ETTTASTEGS ETT/ETTTAS TEGSETT	Novel	Reported	(78)
6	rs1042178	$1.10x10^{-8}$	*HLA-DPA1*	Missense	81	Q/L	Novel	-	-
6	rs9394021	$1.19x10^{-8}$	*VARS2*	Missense	917	R/Q	Novel	-	-
6	rs1126542	$1.20x10^{-8}$	*HLA-DPA1*	Missense	114	T/S	Novel	-	-
6	rs61742983	$1.36x10^{-8}$	*OR5V1*	Missense	233	G/R	Novel	-	-
6	rs3873352	$1.58x10^{-8}$	*HCG22*	Missense	3	R/S	Novel	Reported	(172)
6	rs2308930	$1.61x10^{-8}$	*HLA-DPA1*	Missense	158	L/P	Novel	-	-
6	rs1042308	$1.81x10^{-8}$	*HLA-DPA1*	Missense	191	F/V	Novel	-	-
6	rs61736085	$2.01x10^{-8}$	*POM121L2*	Missense	862	T/I	Novel	-	-
6	rs1140700	$2.10x10^{-8}$	*MICA*	Missense	127	I/K	Novel	Reported	(75)
6	rs9257694	$2.90x10^{-8}$	*OR14J1*	Missense	7	M/T	Novel	-	-
6	rs41266821	$3.02x10^{-8}$	*H4C7*	Missense	3	V/A	Novel	-	-
6	rs2076486	$3.36x10^{-8}$	*UBD*	Missense	95	S/A	Novel	-	-
6	rs2076484	$3.36x10^{-8}$	*UBD*	Missense	51	L/S	Novel	-	-
6	rs2076487	$3.48x10^{-8}$	*UBD*	Missense	99	A/G	Novel	-	-
6	rs16895067	$3.85x10^{-8}$	*OR2I1P*	Missense	174	D/G	Novel	-	-
6	rs16895070	$3.85x10^{-8}$	*OR2I1P*	Missense	188	C/R	Novel	-	-
6	rs7757931	$3.85x10^{-8}$	*UBD*	Missense	162	C/F	Novel	-	-
6	rs1063635	$4.10x10^{-8}$	*MICA*	Missense	165	R/Q	Novel	Reported	(75)
6	rs1126534	$4.49x10^{-8}$	*HLA-DPA1*	Missense	42	A/V	Novel	-	-
6	rs1126533	$4.49x10^{-8}$	*HLA-DPA1*	Missense	42	A/T	Novel	-	-
6	rs1009382	$4.96x10^{-8}$	*TNXB*	Missense	2,518	G/V	Novel	Reported	(168)

SNP, single nucleotide polymorphism.

class II, DM β (*HLA-DMB*) (64), major histocompatibility complex, class II, DQ α1 (*HLA-DQA1*) (65), major histocompatibility complex, class II, DQ α2 (*HLA-DQA2*) (66), major histocompatibility complex, class II, DQ β1 (*HLA-DQB1*) (67), major histocompatibility complex, class II, DR β1 (*HLA-DRB1*) (67), major histocompatibility complex, class I, E (*HLA-E*) (68), major histocompatibility complex, class I, F (*HLA-F*) (69), major histocompatibility complex, class I, G (*HLA-G*) (70), heat shock protein family A (*Hsp70*) member 1A (*HSPA1A/HSPA1B*) (71), Hsp70 member 1-like (71), interleukin 12B (*IL12B*) (72,73), leukocyte specific transcript 1 (74), MHC class I polypeptide-related sequence A (*MICA*) (75), MICA antisense RNA 1 (75), MHC class I polypeptide-related sequence B (*MICB*) (76), MICB divergent transcript (76), myelin oligodendrocyte glycoprotein (77), mucin (*MUC)21* (78), *MUC22* (78), natural cytotoxicity triggering receptor 3 (*NCR3*) (79), negative elongation factor complex member E (80), notch receptor 4 (81-83), nurim (84), psoriasis susceptibility 1 candidate 1 (*PSORS1C1*) (85), *PSORS1C2* (53,54,86), *PSORS1C3* (57), ring finger protein 39 (87), transporter 1, ATP binding cassette subfamily B member (*TAP1*) (64), *TAP2* (64), transcription factor 19 (57), tumor necrosis factor (*TNF*) (88,89), TNFAIP3 interacting protein 1 (*TNIP1*) (60), tenascin XB (*TNXB)* (88,89), tripartite motif containing 10 (*TRIM10*) (90), *TRIM15* (91), *TRIM26* (92), *TRIM27* (92), *TRIM40* (92), TSBP1 and BTNL2 antisense RNA1 (93), ubiquitin D (*UBD*) (94) and ubiquitin-like domain containing CTD phosphatase 1 (95).

HLA genotyping and allele frequency analysis. It is well established that certain HLA alleles and diplotypes are associated with an increased risk of psoriasis. High-resolution imputation was used to analyze the HLA genotypes and their corresponding allele frequencies associated with psoriasis.

Table III. Top 10 HLA diplotypes significantly associated with psoriasis (adjust P<1x10^{-5}).

Rank	HLA genotype (HLA diplotypes)	Adjust P-value	L95	U95	OR	Control	Case	SE	β
1	*HLA-C*01:02-*06:02*	3.59x10^{-19}	3.091	5.286	4.071	481.000	65.000	0.132	1.404
2	*HLA-A*11:01-*33:03*	1.13x10^{-15}	0.289	0.507	0.387	4091.000	53.000	0.138	-0.949
3	*HLA-A*02:07-*11:01*	7.88x10^{-11}	1.453	1.961	1.692	3389.000	190.000	0.075	0.526
4	*HLA-A*02:07-*30:01*	6.92x10^{-10}	2.939	6.905	4.587	177.000	27.000	0.207	1.523
5	*HLA-B*13:02-*46:01*	8.92x10^{-10}	2.646	5.813	3.985	234.000	31.000	0.191	1.382
6	*HLA-C*06:02-*12:02*	7.48x10^{-9}	3.365	9.598	5.827	98.000	19.000	0.251	1.763
7	*HLA-DQB1*02:01-*03:01*	2.41x10^{-7}	0.326	0.643	0.465	2384.000	37.000	0.166	-0.766
8	*HLA-B*46:01-*46:01*	9.27x10^{-7}	1.506	2.482	1.947	1082.000	70.000	0.124	0.666
9	*HLA-B*46:01-*57:01*	1.60x10^{-6}	4.143	21.944	10.017	27.000	9.000	0.385	2.304
10	*HLA-A*24:02-*33:03*	1.67x10^{-6}	0.369	0.692	0.512	2517.000	43.000	0.154	-0.670

HLA, human leukocyte antigen; OR, odds ratio; SE, standard error; L95, lower 95% confidence interval; U95, upper 95% confidence interval.

Table IV. Top 10 HLA allele frequencies significantly associated with psoriasis (adjust P<1x10^{-5}).

Rank	Allele frequency (HLA haplotypes)	Adjust P-value	L95	U95	OR	Control	Case	SE	β
1	*HLA-A*02:07*	3.69x10^{-34}	1.602	1.894	1.743	10510.000	605.000	0.042	0.556
2	*HLA-C*06:02*	2.96x10^{-29}	2.205	2.964	2.563	2341.000	199.000	0.074	0.941
3	*HLA-B*46:01*	7.19x10^{-22}	1.396	1.640	1.514	12905.000	646.000	0.041	0.415
4	*HLA-A*33:03*	5.02x10^{-21}	0.503	0.650	0.573	12818.000	246.000	0.065	-0.557
5	*HLA-C*03:02*	5.11x10^{-17}	0.545	0.697	0.617	13015.000	269.000	0.062	-0.482
6	*HLA-B*13:02*	5.42x10^{-15}	1.923	2.844	2.348	1461.000	114.000	0.097	0.854
7	*HLA-B*58:01*	9.21x10^{-13}	0.567	0.735	0.647	11230.000	243.000	0.065	-0.435
8	*HLA-C*01:02*	8.44x10^{-12}	1.191	1.365	1.276	21439.000	905.000	0.034	0.244
9	*HLA-DQA1*02:01*	1.13x10^{-11}	1.606	2.282	1.921	2178.000	139.000	0.088	0.653
10	*HLA-DQB1*02:02*	2.53x10^{-11}	1.573	2.223	1.876	2294.000	143.000	0.086	0.629

HLA, human leukocyte antigen; OR, odds ratio; SE, standard error; L95, lower 95% confidence interval; U95, upper 95% confidence interval.

Table III shows the diplotypes identified in the sample and those that exhibited a significant association with psoriasis are listed in Table IV. Table SII presents raw data regarding HLA genotypes and allele frequencies that were significantly associated with psoriasis. The findings of the present study indicated that the *HLA-A*02:07* (adjusted P=3.69x10^{-34}) and *HLA-C*06:02* (adjusted P=2.96x10^{-29}) alleles exhibited the strongest association with psoriasis in the Taiwanese population.

Network analysis of SNPs associated with psoriasis on GWAS models. A comprehensive analysis was carried out using Bioinformatics IPA software to analyze 8,585 SNPs associated with psoriasis. These SNPs were assessed for significance in the context of the entire genome, using a threshold of P<5x10^{-8}. The present study findings revealed that psoriasis is characterized by multiple key pathways, including immune responses (antigen presentation, PD-1/PD-L1 cancer immunotherapy, IL-10 signaling, interplay between dendritic cells and natural killer cells and Th1/Th2 activation) and inflammatory signaling (multiple sclerosis and neuroinflammatory signaling pathways), which are shown in Table V. Furthermore, gene numbers were cross-analyzed with pathways, resulting in the ranking of various biological processes: Cellular immune response, humoral immune response, cytokine signaling, cancer, disease-specific pathways, neurotransmitters and nervous system signaling, cellular growth, proliferation and development of neurotransmitters, pathogen-influenced signaling, cellular stress and injury, intracellular and second messenger signaling, apoptosis, organismal growth and development, nuclear receptor signaling, biosynthesis, and metabolic clusters (Fig. 3). Our GWAS and network analysis findings suggested that the diversity of specific genes, including *HLA-A, HLA-C, HLA-DM, HLA-DP, HLA-DQ*, psoriasis susceptibility 1 *(PSORS1)*, HLA complex group on chromosome 6 and *IL-12B* on chromosome 5, play a crucial role in the development of psoriasis (Fig. 4A). Additionally, our results showed significant association with psoriasis between

Table V. Canonical network analysis of GWAS results in psoriasis ($P<5x10^{-8}$).

Ingenuity canonical pathways	-log (P-value)	Molecules
Antigen presentation pathway	27.8	*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DMB*, *HLA-DOB*, *HLA-DPA1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRB1*, *HLA-E*, *HLA-F*, *HLA-G*, *PSMB9*, *TAP1*, *TAP2*
PD-1, PD-L1 cancer immunotherapy pathway	17.7	*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DMB*, *HLA-DOB*, *HLA-DPA1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRB1*, *HLA-E*, *HLA-F*, *HLA-G*, *IL12B*, *TNF*
Multiple sclerosis signaling pathway	15.1	*C2*, *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DMB*, *HLA-DOB*, *HLA-DPA1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRB1*, *HLA-E*, *HLA-F*, *HLA-G*, *IL12B*, *MOG*, *TNF*
IL-10 signaling	13.8	*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DMB*, *HLA-DOB*, *HLA-DPA1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRB1*, *HLA-E*, *HLA-F*, *HLA-G*, *TNF*
Crosstalk between dendritic cells and natural killer cells	12.7	*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-E*, *HLA-F*, *HLA-G*, *IL12B*, *MICA*, *MICB*, *NCR3*, *TNF*, *HSPA1A/HSPA1B*, *HSPA1L*
Neuroinflammation signaling pathway	12.4	*AGER*, *GABBR1*, *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DMB*, *HLA-DOB*, *HLA-DPA1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRB1*, *HLA-E*, *HLA-F*, *HLA-G*, *IL12B*, *TNF*
Th1 and Th2 pathway	9.43	*HLA-A*, *HLA-B*, *HLA-DMB*, *HLA-DOB*, *HLA-DPA1*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *HLA-DRB1*, *IL12B*, *NOTCH4*

GWAS, genome-wide association study. PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; IL-10, interleukin 10; Th, T helper.

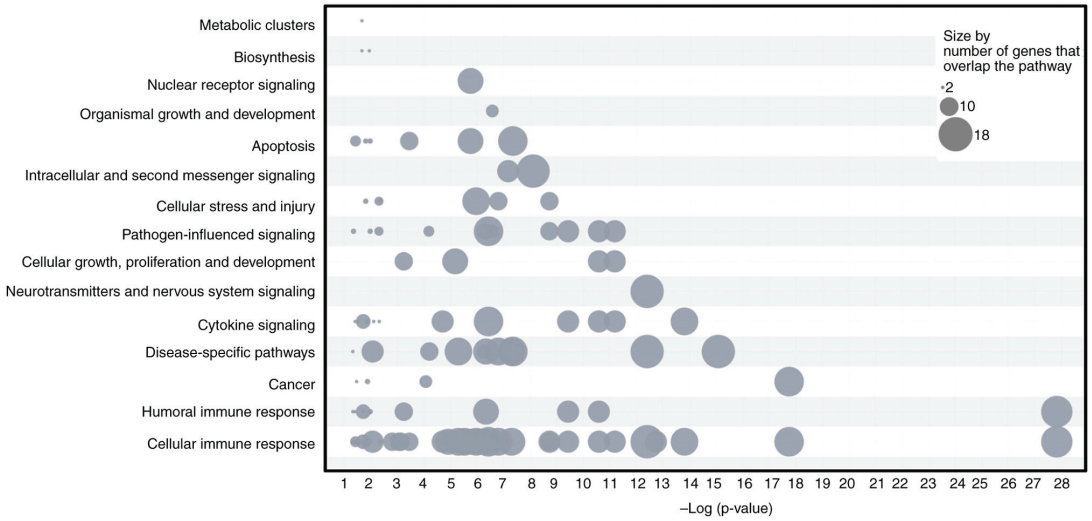


Figure 3. Bioinformatics network analysis of 1,684 SNP gene locations of the genome-wide association study that are associated with psoriasis, and cross analysis of the number of genes and pathways (SNP gene loci, $P<5x10^{-8}$). SNP, single nucleotide polymorphism.

AGER, discoidin domain receptor tyrosine kinase 1 (*DDR1*), TNF, coiled-coil α-helical rod protein 1 (*CCHCR1*), tubulin β class I (*TUBB*) and *TNXB* genes (Fig. 4B). Furthermore, the regional association plot (linkage disequilibrium score $r^2>0.4$)

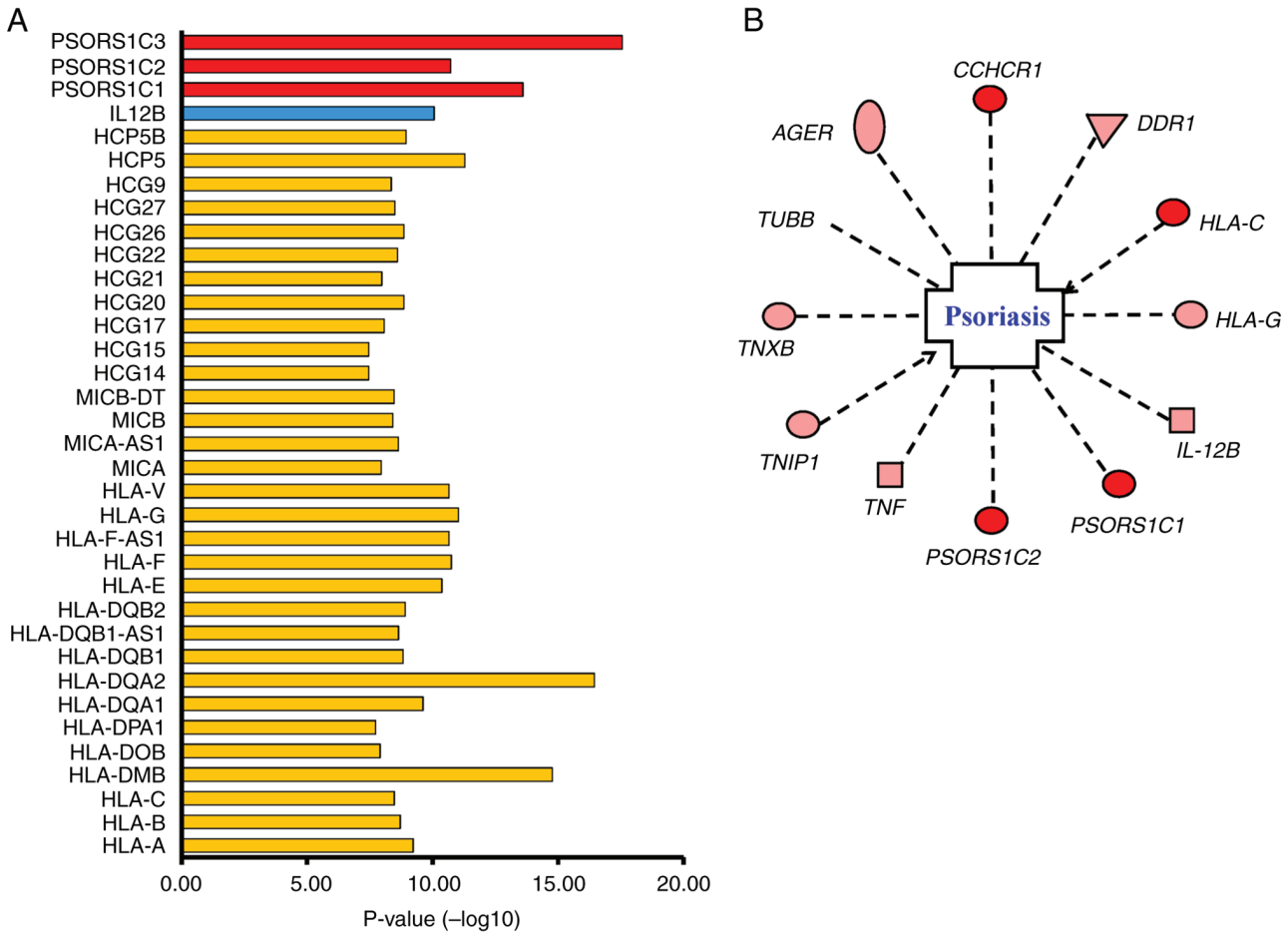
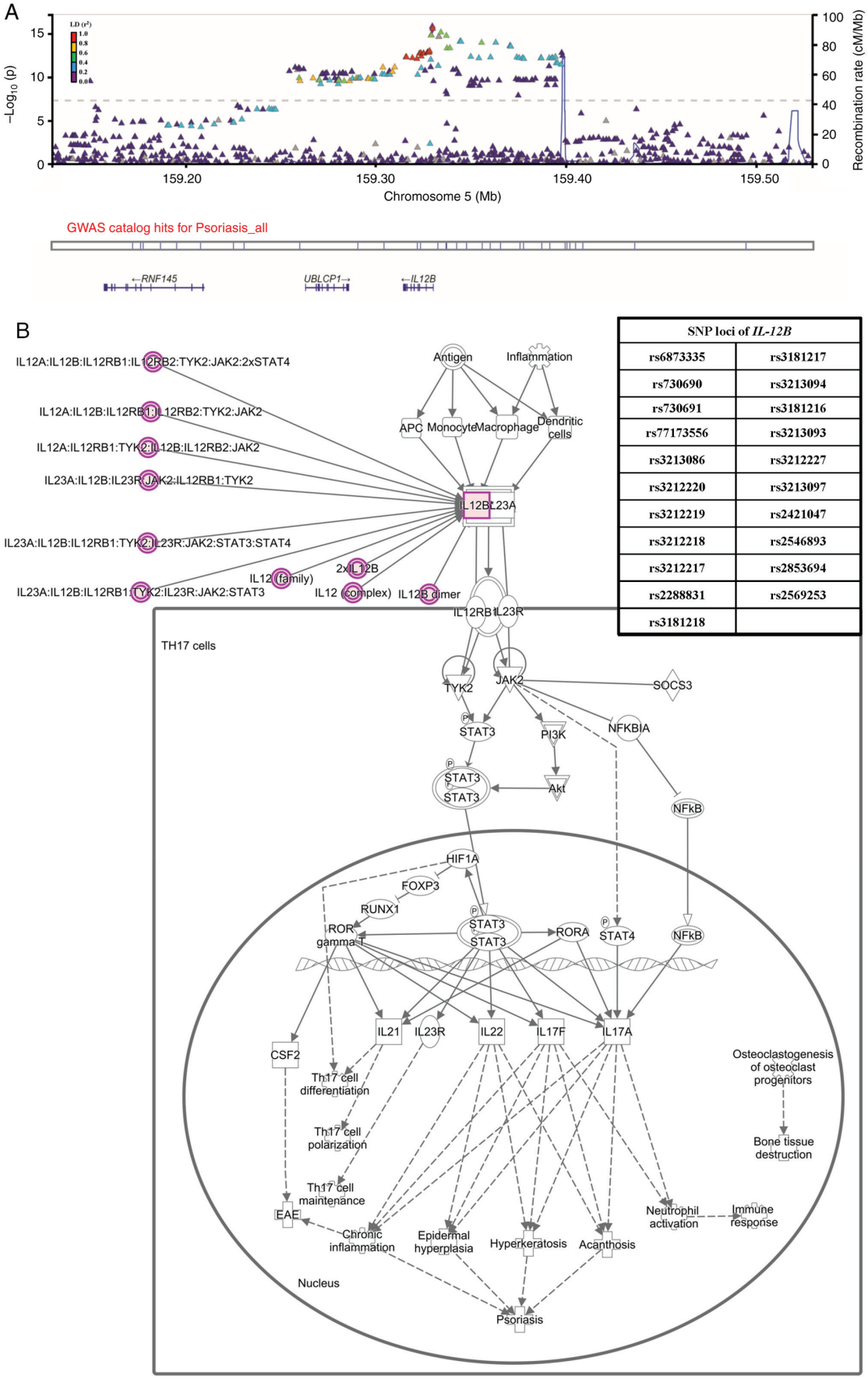


Figure 4. Network analysis of single nucleotide polymorphisms associated with psoriasis using genome-wide association study models. (A) Summary of the *HLA*-related genes, *IL-12B* and *PSORS1* in psoriasis by GWAS analysis ($P<5x10^{-8}$). (B) Related genetic markers (*PSORS1C1, PSORS1C2, IL-12B, TNF, CCHCR1, AGER, DDR1, TUBB, TNIP1, HLA-C, HLA-G* and *TNXB*) associated with psoriasis. GWAS, genome-wide association study; HLA, Human leukocyte antigen; IL-12B, interleukin 12B; PSORS1, psoriasis susceptibility 1; PSORS1C1, psoriasis susceptibility 1 candidate 1; PSORS1C2, psoriasis susceptibility 1 candidate 2; TNF, tumor necrosis factor; CCHCR1, coiled-coil α-helical rod protein 1; AGER, advanced glycosylation end-product specific receptor; DDR1, discoidin domain receptor tyrosine kinase 1; TUBB, tubulin β class I; TNIP1, TNFAIP3 interacting protein 1; HLA-C, major histocompatibility complex, class I, C; HLA-G, major histocompatibility complex, class I, G; TNXB, tenascin XB.

demonstrated a strong association between variations in the *IL12B* gene and psoriasis (Fig. 5A). Finally, the psoriasis model regulated by the IL12B/IL23 signaling pathway was analyzed using the IPA database (Fig. 5B). The analysis confirmed the presence of multiple highly correlated *IL12B* genes and SNP sites, thereby providing substantial evidence to support the existence of the IL-12 pathway.

PRS model for predicting the risks of psoriasis and associated comorbidities. To analyze the PRSs for psoriasis, the dataset was divided into three sections: Base, target and validation, at a ratio of 8:1:1. Each group was treated as a separate entity. Summary statistics were calculated using data from the base group, and a model was constructed using data from the target group. Data from the validation group were used to assess the accuracy of the model. A total of 1,684 SNPs with a significance level of P<0.001 were chosen from a pool of 865 genes. The raw data for the PRS models are presented in Table SIII. Fig. 6A and B illustrate the PRS distribution and statistical findings applicable to the target and validation groups. Fig. 6C shows the receiver operating characteristic curve of the PRS for the prediction of psoriasis. The data indicated that patients with psoriasis exhibited a significantly higher PRS than those in the control group (P<0.001). Table VI presents an analysis of the area under the curve (AUC) for the PRS for psoriasis. The AUC of the PRS alone model was 0.611 [95% confidence interval (CI), 0.584-0.638], while that of the PRS with age and sex combined was 0.611 (95% CI, 0.584-0.638). In addition, the AUC of PRS with *HLA-A*02:07* and *HLA-C*06:02* combined was 0.598 (95% CI, 0.571-0.624), while that of PRS combined with age, sex, *HLA-A*02:07* and *HLA-C*06:02* was 0.629 (95% CI, 0.602-0.656). It was demonstrated that these SNPs collectively represent major risk factors for the development of psoriasis. Furthermore, *HLA-A*02:07* and *HLA-C*06:02* provided considerable discriminatory ability, making a significant contribution to the risk of psoriasis.

Genetic associations between SNPs and various human phenotypes in a PRS model. Psoriasis and various human disorders have been studied using PheWAS. Fig. 7 and Table VII provide an overview of the genetic associations between psoriasis and the other diseases. The three diseases that showed the strongest association with PRS are dermatologic, infectious and musculoskeletal conditions. The present



SNP loci of *IL-12B*	
rs6873335	rs3181217
rs730690	rs3213094
rs730691	rs3181216
rs77173556	rs3213093
rs3213086	rs3212227
rs3212220	rs3213097
rs3212219	rs2421047
rs3212218	rs2546893
rs3212217	rs2853694
rs2288831	rs2569253
rs3181218	

Figure 5. Regional association plot showing signals around chromosomal 5 for the GWAS of psoriasis. (A) Regional association plot of the *IL-12B* gene in psoriasis. The regional plot showed significant differences in effect-size estimates. The plot typically shows the position of each SNP along the x-axis and negative log10 P-value. The color of the point was used to show the linkage disequilibrium between SNPs. (B) Pathway diagram depicting *IL-12B* involving genes that are significantly associated with psoriasis (SNPs gene loci, $P<5x10^{-8}$). GWAS, genome-wide association study; SNP, single nucleotide polymorphism; IL-12B, interleukin 12B; UBLCP1, ubiquitin-like domain-containing CTD phosphatase 1; RNF145, ring finger protein 145.

Table VI. Area under the curve analysis of PRS in psoriasis.

Test result variable (s)	Area	Standard error[a]	Asymptotic significance[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
PRS	0.611	0.014	0.000	0.584	0.638
PRS_Age_Sex	0.611	0.014	0.000	0.584	0.638
PRS_ *HLA-A*02:07_ HLA-C*06:02*	0.598	0.014	0.000	0.571	0.624
PRS_Age_Sex_*HLA-A*02:07_ HLA-C*06:02*	0.629	0.014	0.000	0.602	0.656

The test result variable (s): PRS_ PSA. PRS has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a]Under the nonparametric assumption; [b]null hypothesis: True area =0.5.

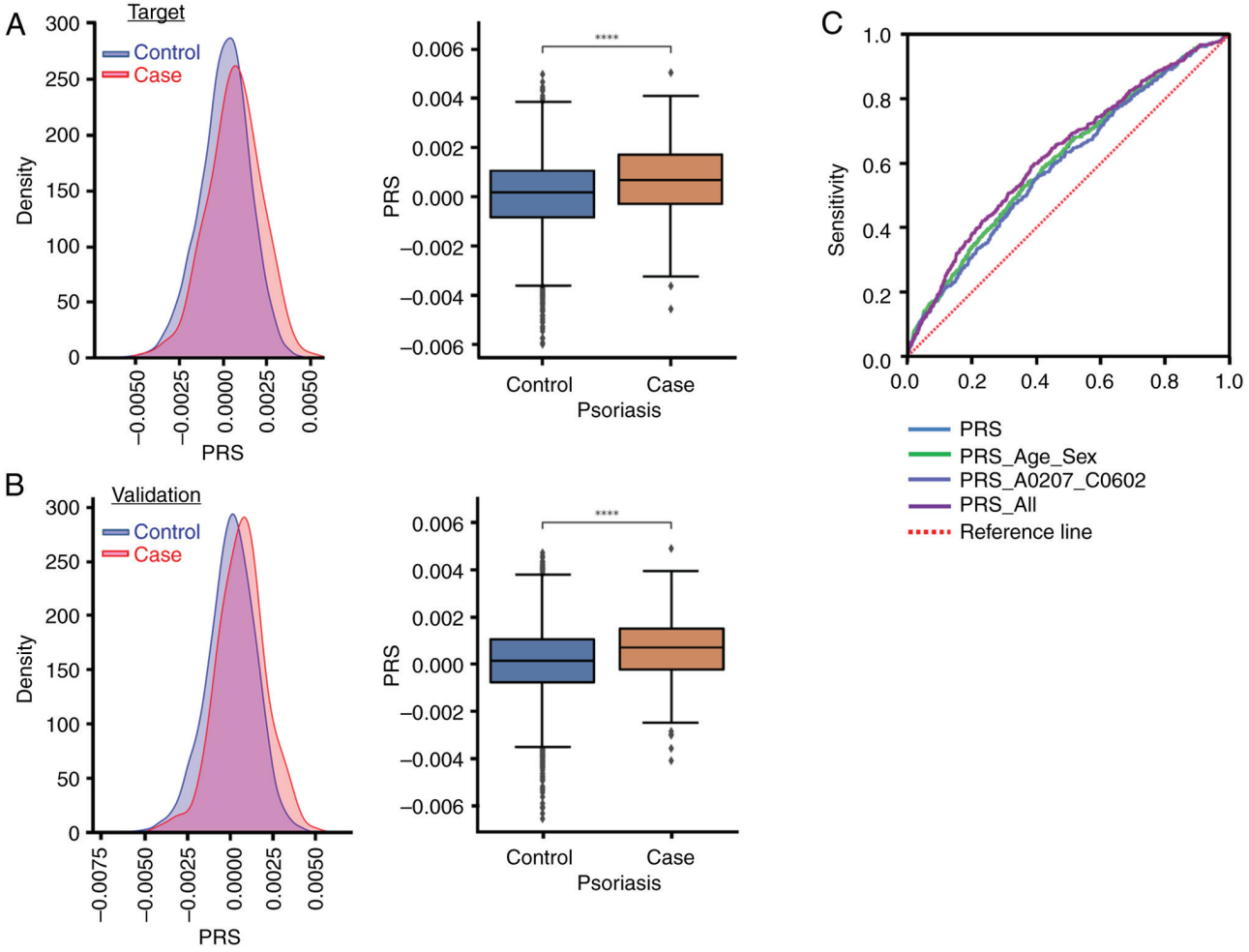


Figure 6. Distribution of the PRS and corresponding statistical results in psoriasis. Distribution of the PRS and corresponding statistical results in the (A) target and (B) validation groups. (C) The ROC curve of the PRS for the prediction of psoriasis. The colors represent different diseases and biomarkers (****P<0.001). ROC, receiver operator characteristic; PRS, polygenic risk score.

study serves as a crucial clinical benchmark for the treatment of psoriasis. Furthermore, the PheWAS results demonstrated a genetic association between psoriasis and various diseases.

Meta-analysis by the BBJ. Finally, a meta-analysis was conducted in collaboration with the BBJ to investigate the genetic relationships within the East Asian population with respect to psoriasis. The psoriasis GWAS from Biobank Japan (BBJ) was published previously (29). The summary statistics of psoriasis were downloaded from BBJ to replicate our results. Table SIV presents unprocessed results from the meta-analysis of SNPs. Upon completion of the meta-analysis, the top 20 SNPs retained their genome-wide significance (Table VIII). In the BBJ cohort, results identified 438 significant single

Table VII. PheWAS of SNP loci from PRS in psoriasis.

A, Dermatological disease

Phecode	Description	Cases	Controls	P-value	OR
696.4	Psoriasis	1,693	58,813	$0.00x10^{00}$	Infinity
696	Psoriasis and related disorders	1,753	58,813	$0.00x10^{00}$	Infinity
696.41	Psoriasis vulgaris	1,518	58,813	$0.00x10^{00}$	Infinity
696.42	Psoriatic arthropathy	709	58,813	$0.00x10^{00}$	Infinity
939	Atopic/contact dermatitis due to other or unspecified	4,095	54,969	$3.32x10^{-49}$	$7.63x10^{69}$
695	Erythematous conditions	1,316	59,656	$1.64x10^{-37}$	$1.31x10^{111}$
706.8	Other specified diseases of sebaceous glands	317	62,272	$8.64x10^{-31}$	$2.09x10^{188}$
709.2	Sicca syndrome	212	58,921	$3.86x10^{-30}$	$6.50x10^{254}$
690	Erythematosquamous dermatosis	725	59,656	$4.23x10^{-29}$	$2.70x10^{131}$
686.5	Pyoderma	675	55,568	$1.56x10^{-28}$	$9.99x10^{125}$
690.1	Seborrheic dermatitis	637	59,656	$8.22x10^{-26}$	$3.48x10^{131}$
709	Diffuse diseases of connective tissue	527	58,921	$2.99x10^{-23}$	$1.35x10^{137}$
706	Diseases of sebaceous glands	1,377	62,272	$7.74x10^{-23}$	$2.20x10^{78}$
695.42	Systemic lupus erythematosus	125	59,651	$9.71x10^{-22}$	$1.59x10^{279}$
704.8	Other specified diseases of hair and hair follicles	571	63,275	$1.16x10^{-21}$	$1.35x10^{117}$
695.4	Lupus (localized and systemic)	168	59,651	$3.58x10^{-20}$	$2.14x10^{229}$
686	Other local infections of skin and subcutaneous tissue	2,139	55,568	$4.86x10^{-19}$	$2.30x10^{57}$
696.2	Parapsoriasis	47	59,656	$1.89x10^{-17}$	Infinity
704	Diseases of hair and hair follicles	899	63,275	$3.38x10^{-15}$	$1.30x10^{77}$
695.7	Prurigo and Lichen	858	59,656	$4.23x10^{-15}$	$3.68x10^{83}$
698	Pruritus and related conditions	415	64,546	$1.28x10^{-10}$	$1.23x10^{92}$
701.1	Keratoderma, acquired	138	64,131	$7.17x10^{-9}$	$6.06x10^{142}$
706.1	Acne	968	62,272	$2.13x10^{-8}$	$8.69x10^{52}$
695.2	Bullous dermatoses	103	59,656	$1.09x10^{-7}$	$2.13x10^{167}$
705.1	Dyshidrosis	183	62,272	$3.00x10^{-7}$	$1.53x10^{111}$
696.3	Pityriasis	33	59,656	$3.81x10^{-7}$	$1.29x10^{289}$
701	Other hypertrophic and atrophic conditions of skin	613	64,131	$1.24x10^{-6}$	$1.44x10^{57}$
705	Disorders of sweat glands	221	62,272	$3.46x10^{-6}$	$4.95x10^{91}$
681	Superficial cellulitis and abscess	3,667	55,568	$4.48x10^{-6}$	$5.32x10^{22}$
695.3	Rosacea	94	59,656	$6.48x10^{-6}$	$4.13x10^{147}$
695.22	Pemphigus and pemphigoid	61	59,656	$1.35x10^{-5}$	$4.93x10^{178}$
703	Diseases of nail, NOS	60	63,275	$1.63x10^{-5}$	$3.17x10^{161}$
947	Urticaria	1,624	54,969	$9.10x10^{-10}$	$1.95x10^{45}$

B, Infectious diseases

Phecode	Description	Cases	Controls	P-value	OR
110.1	Dermatophytosis	1,439	61,270	$6.03x10^{-29}$	$1.31x10^{87}$
110	Dermatophytosis/Dermatomycosis	1,585	61,270	$1.09x10^{-26}$	$3.43x10^{79}$
110.12	Athlete's foot	770	61,270	$3.09x10^{-19}$	$2.38x10^{95}$
110.11	Dermatophytosis of nail	621	61,270	$4.59x10^{-18}$	$3.57x10^{102}$
110.13	Dermatophytosis of the body	406	61,270	$7.40x10^{-17}$	$5.03x10^{121}$
78	Viral warts and HPV	737	50,808	$4.44x10^{-7}$	$4.35x10^{54}$
53	Herpes zoster	932	50,808	$5.32x10^{-7}$	$2.23x10^{48}$
54	Herpes simplex	554	50,808	$1.17x10^{-6}$	$6.30x10^{60}$

C, Musculoskeletal disease

Phecode	Description	Cases	Controls	P-value	OR
714.1	Rheumatoid arthritis	156	60,426	$1.01x10^{-26}$	$3.32x10^{279}$

Table VII. Continued.

C, Musculoskeletal disease

Phecode	Description	Cases	Controls	P-value	OR
715.2	Ankylosing spondylitis	124	60,426	$1.36x10^{-15}$	$1.38x10^{232}$
714	Rheumatoid arthritis and other inflammatory polyarthropathies	540	60,426	$1.42x10^{-14}$	$6.14x10^{103}$
715	Other inflammatory spondylopathies	182	60,426	$1.42x10^{-12}$	$1.21x10^{167}$
721.8	Other allied disorders of spine	98	57,268	$4.74x10^{-10}$	$1.78x10^{180}$
740.1	Osteoarthritis; localized	2,164	59,489	$7.61x10^{-8}$	$1.16x10^{34}$
740.11	Osteoarthrosis, localized, primary	1,624	59,489	$1.05x10^{-7}$	$5.91x10^{38}$
716	Other arthropathies	1,082	61,357	$2.09x10^{-6}$	$2.64x10^{42}$

D, Endocrine/metabolic disease

Phecode	Description	Cases	Controls	P-value	OR
242	Thyrotoxicosis with or without goiter	1,743	58,192	$2.79x10^{-7}$	$1.63x10^{36}$
279.1	Immunity deficiency	101	64,597	$1.13x10^{-6}$	$1.48x10^{140}$
250.1	Type 1 diabetes	354	53,008	$4.32x10^{-6}$	$1.98x10^{-69}$
250.11	Type 1 diabetes with ketoacidosis	90	53,008	$8.82x10^{-6}$	$2.91x10^{-128}$
279	Disorders involving the immune mechanism	563	64,597	$1.61x10^{-5}$	$9.35x10^{52}$

E, Circulatory system disease

Phecode	Description	Cases	Controls	P-value	OR
446.3	Hypersensitivity angiitis	49	63,133	$2.64x10^{-6}$	$1.59x10^{191}$
446	Polyarteritis nodosa and allied conditions	172	63,133	$3.41x10^{-6}$	$1.18x10^{103}$

F, Hematopoietic disease

Phecode	Description	Cases	Controls	P-value	OR
289	Other diseases of blood and blood-forming organs	264	62,279	$1.04x10^{-6}$	$1.13x10^{79}$
286.81	Primary hypercoagulable state	144	64,206	$3.22x10^{-6}$	$7.74x10^{100}$

OR, odds ratio; PheWAS, phenome-wide association study; SNP, single nucleotide polymorphism; PRS, polygenic risk score; HPV, human papillomavirus.

nucleotide polymorphisms associated with psoriasis, with a significance level of $P<1x10^{-5}$. The majority of these SNPs are located on chromosome 6. By conducting a meta-analysis of the GWAS at key SNP sites within the BBJ Cohort, the persistent significance of these SNPs wAS confirmed. This validates the robustness and reliability of the present findings.

Discussion

Psoriasis is a complex disease involving various pathogenic and immunological mechanisms (17,96). Although >100 psoriasis susceptibility loci have been identified through GWAS in different countries and ethnicities (96-101), there have been limited studies on genetic susceptibility loci in Taiwan (102,103). The present study conducted GWAS and PRS to identify 92 novel genomic markers and identified 61 previously reported genomic markers associated with psoriasis. Through network analysis, several biological processes were discovered that contribute to psoriasis. These processes involve factors such as HLA subtypes and genetic SNPs that affect cytokines, and the *PSORS1* locus. Additionally, it is possible that transcriptional regulators and shared pathogenic processes as well as other human diseases are involved in the development of psoriasis.

The immune response plays an important role in the development of psoriasis, and HLA polymorphisms have been implicated in this process (104,105). Major histocompatibility complex (MHC) molecules are present on every cell and

Table VIII. Meta-analysis of SNP loci on psoriasis in CMUH and BBJ studies.

				CMUH			BBJ			Meta-analysis		
CHR	SNP	REF	ALT	β	SE	P-value	β	SE	P-value	β	SE	P-value
6	rs1634774	A	G	0.494	0.034	$7.19x10^{-47}$	0.366	0.114	0.001	0.483	0.033	$7.36x10^{-49}$
6	rs9380151	T	C	0.609	0.044	$2.40x10^{-43}$	0.958	0.244	$8.55x10^{-5}$	0.620	0.043	$2.79x10^{-46}$
6	rs9368611	A	C	0.621	0.045	$3.09x10^{-43}$	1.354	0.299	$5.78x10^{-6}$	0.637	0.045	$1.95x10^{-46}$
6	rs75791723	C	T	0.605	0.045	$5.48x10^{-42}$	1.235	0.267	$3.58x10^{-6}$	-0.623	0.044	$1.73x10^{-45}$
6	rs4997405	C	T	0.465	0.035	$3.00x10^{-41}$	-0.137	0.099	0.165	-0.400	0.033	$1.97x10^{-34}$
6	rs2596521	A	G	0.456	0.034	$6.38x10^{-41}$	0.467	0.103	$5.68x10^{-6}$	0.457	0.032	$2.05x10^{-45}$
6	rs9391847	A	G	0.456	0.034	$9.99x10^{-41}$	0.475	0.103	$4.04x10^{-6}$	0.458	0.032	$2.34x10^{-45}$
6	rs2523624	G	A	0.454	0.034	$1.05x10^{-40}$	0.467	0.103	$5.62x10^{-6}$	-0.456	0.032	$3.33x10^{-45}$
6	rs3132482	G	A	-0.463	0.035	$1.75x10^{-39}$	-0.085	0.099	0.393	0.421	0.033	$7.72x10^{-37}$
6	rs9263986	A	G	0.453	0.034	$1.86x10^{-39}$	0.014	0.102	0.889	0.408	0.033	$7.94x10^{-36}$
6	rs3868082	A	G	-0.453	0.035	$1.15x10^{-38}$	-0.146	0.099	0.138	-0.419	0.033	$2.84x10^{-37}$
6	rs9393991	G	A	0.576	0.044	$1.70x10^{-38}$	0.968	0.247	$9.22x10^{-5}$	-0.589	0.044	$2.63x10^{-41}$
6	rs117565607	T	A	0.577	0.045	$2.51x10^{-38}$	1.092	0.265	$3.66x10^{-5}$	-0.591	0.044	$3.04x10^{-41}$
6	rs6927080	C	G	0.444	0.034	$7.28x10^{-38}$	0.026	0.102	0.797	0.401	0.033	$1.42x10^{-34}$
6	rs9391681	T	C	0.578	0.045	$8.59x10^{-38}$	1.279	0.286	$7.57x10^{-6}$	0.595	0.045	$6.91x10^{-41}$
6	rs117416277	T	C	0.573	0.045	$1.53x10^{-38}$	0.968	0.237	$4.44x10^{-5}$	0.586	0.044	$1.35x10^{-40}$
6	rs3132484	G	T	-0.462	0.036	$2.64x10^{-37}$	-0.105	0.101	0.296	0.421	0.034	$3.96x10^{-35}$
6	rs3132483	G	A	-0.462	0.036	$2.64x10^{-37}$	-0.105	0.101	0.296	0.421	0.034	$3.96x10^{-35}$
6	rs3132485	C	A	-0.462	0.036	$2.65x10^{-37}$	-0.106	0.101	0.294	0.421	0.034	$3.93x10^{-35}$
6	rs12194291	G	C	0.545	0.043	$3.36x10^{-37}$	0.957	0.214	$7.81x10^{-6}$	-0.561	0.042	$8.70x10^{-41}$

CHR, chromosome; POS, position; REF, reference allele; ALT, alternative allele; CMUH, China Medical University Hospital; BBJ, Biobank Japan; SNP, single nucleotide polymorphism; SE, standard error.

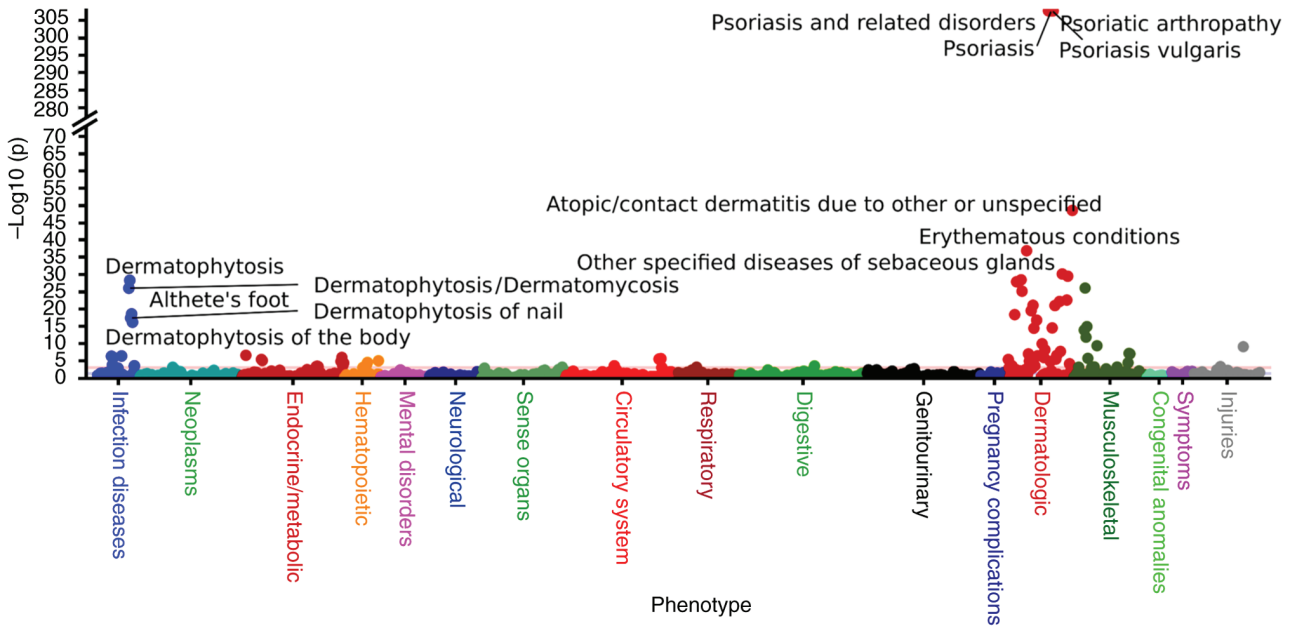


Figure 7. PheWAS analysis of the association between SNPs loci from PRS and human disease (SNPs gene loci, denoting a P<0.001). PheWAS, phenome-wide association; SNP, single-nucleotide polymorphism; PRS, polygenic risk score.

provide peptide antigens to $CD4^+$ and $CD8^+$ T cells (106,107). The length of these antigens is usually 8-10 amino acids (108). The presence of HLA polymorphisms leads to variable peptide-binding grooves that contain two or three specific acceptor sites or pockets (109). HLA molecules present a variety of antigenic peptides by binding to specific amino acid side

chains (110). The acceptor sites on HLA molecules differ from one another, resulting in different peptide repertoires being presented for different HLA molecules (109,110). The antigenic peptides contained in each HLA molecule are unique, despite some overlap in binding specificities (111,112). Certain HLA alleles, such as *HLA-A* (61), *HLA-B* (62,63), *HLA-C* (53,54), *HLA-DMB* (64), *HLA-DQA1* (65), *HLA-DQA2* (66), *HLA-DQB1* (67), *HLA-DRB1* (67), *HLA-E* (68), *HLA-F* (69) and *HLA-G* (70), are more prevalent in patients with psoriasis. The findings of the present study indicated a significant association between the genetic variability of *HLA*-related genes located on chromosome 6 and the development of psoriasis. It was confirmed that certain *HLA* genes, including *HLA-DPA1, HLA-E, HLA-F, HLA-G, MICA* and *MICB* have amino acid mutations (68,113-115). The findings from the present study indicated a notable association between *HLA-A*02:07* and *HLA-C*06:02* alleles and psoriasis in the Taiwanese population. The *HLA-C*06:02* allele is the most prominent risk factor for psoriasis (116-119). The risk allele frequencies of psoriasis have been reported to be 6-17% in Taiwan, 8-26% in Japan, 76.1% in Korea, 14% in Thailand and 46-67% in Caucasian populations (120). Shen *et al* demonstrated a significant association between psoriasis and certain HLA alleles, including *HLA-A*02:07* and *HLA-C*06:02,* in Chinese patients with psoriasis in Singapore (121). Furthermore, the *HLA-A*02:07* allele is significantly associated with the development of psoriasis in individuals residing in southern China (122). In Japan, psoriasis vulgaris has been reported to be associated with *HLA-A*02:07* and *HLA-C*06:02* alleles (123). The *HLA-Cw*06* allele is associated with the highest degree of susceptibility to psoriasis (116,124,125). It associates with the occurrence of psoriasis as well as with improved treatment outcomes with methotrexate, IL-12, IL-17 and IL-23 targeted therapeutic agents (126). Furthermore, *HLA-C*06:02* has been identified as a biomarker for predicting the response to biological treatment in patients with psoriasis (116). The present study also suggested that *HLA-A*02:07* and *HLA-C*06:02* significantly contribute to the risk of psoriasis, as demonstrated by the PRS analysis.

Pro-inflammatory cytokines, including IL-12, IL-23 and TNF, play crucial roles in the development and progression of psoriasis (72). IL-12B/IL-23 and TNF are involved in inflammatory processes (72). *IL-12B* encodes for a subunit of IL-12. IL-12 is a disulfide-linked heterodimer consisting of two subunits: A 40 kD cytokine receptor-like subunit encoded by *IL-12B* and a 35 kD subunit encoded by *IL-12A* (127). IL-12 exerts its effects on T and natural killer cells, leading to the activation of these immune cell populations (128). It is expressed by activated macrophages, which play a crucial role in Th1 cell development. IL-12 is essential for maintaining an adequate number of memory/effector Th1 cells to provide long-term protection against intracellular pathogens (129). IL-23 cytokines are composed of two subunits, IL-23A and IL-12B, both of which play significant roles in various biological functions (127). IL-12B and IL-23 are particularly important in the differentiation of T cells, specifically, the generation of Th1 cells that produce IFN-γ and Th17 cells that produce IL-17 (72). Previously, it was observed that IL-12 is overexpressed on dendritic cells in the skin lesions of patients with psoriasis (130). Moreover, ustekinumab, an FDA-approved monoclonal antibody targeting IL-12/23p40, has shown great efficacy in treating patients with psoriasis (99,131). In the present study a strong association between variations in *IL-12B* levels was identified in the psoriasis group. Previous studies identified several SNPs associated with psoriasis in genes such as *IL-12* (rs3212220, rs3212217 and rs3212227), *IL-23*/*IL-23R* and *IL-17* (89,132). However, the present study did not find any polymorphisms at the SNP loci of *IL-23* or *IL-17*. Overall, our findings suggested that *IL-12B* and its associated SNPs on chromosome 5 are important in the pathogenesis of psoriasis. Further investigation of these pathways may provide valuable insights into the mechanisms underlying the disease.

Previous studies have shown that HSPA1A/HSPA1B and TRIM15 play roles in the pathogenesis of psoriasis (71,91). HSPA1A and HSPA1B are heat shock proteins that regulate the secretion of TNF-α, IL-1β and IL-10 from monocytes (133). TRIM15, on the other hand, stimulates TNF-α and is involved in the TNF-α/NF-κB pathway, contributing to the inflammatory response (91). In the present study psoriasis was associated with SNPs in *TNF* (rs1800629) and *TNIP1* (rs76956521, rs2233278, rs75851973 and rs8177833). Our study established a connection between *HSPA1A*/*HSPA1B*, *TRIM15* and psoriasis. Additionally, several genes associated with enzymes and kinases were identified including *AGPAT1, ATAT1, BAG6, CARMIL1, DHX16, DDAH2*, *GPX5, GPX6, NEU1*, *PGBD1, PPP1R11*, *SKIC2*, *VARS1* and *VARS2,* as SNP loci. Currently, there is no definitive evidence linking enzymatic activity with psoriasis, which requires further investigation. Future studies should, therefore, prioritize research on these genes.

Familial recurrence of psoriasis has been extensively studied, and it has been found that monozygotic twins are more likely to have the disease than dizygotic twins (134). The main genetic factor responsible for psoriasis is *PSORS1*, which is located within the MHC on chromosome 6p21.3 (135,136). This region spans a range of 80-250 kb (137). The *PSORS1* locus contains several genes including *HLA-C, MICA*, *PSORS1C3* and *CDSN*. These candidate genes have alleles within the *PSORS1* locus and have been shown to be expressed in skin cells (138). HLA-C is responsible for presenting peptides to cytotoxic T cells ($CD8^+$T cells) by interacting with them on the cell membrane, which activates the immune response and cytotoxicity of cytotoxic T cells (139). MICA is a cell-surface glycoprotein encoded by the *MICA* gene located within the MHC locus. It is recognized by NK cells, γδ T cells and $CD8^+$ αβ T cells, which carry the NKG2D receptor on their cell surfaces (140). CDSN is primarily expressed in the upper layers of epidermis and hair follicles. It contributes to keratinocyte cohesion, and is targeted by proteases during epidermal desquamation (141). *PSORS1C3* is a non-coding gene and its RNA transcript is found in patients with psoriasis. The functional role of *PSORS1C3* is to modulate the inflammatory response (142). An association between *PSORS1C3* polymorphisms and psoriasis has been reported in various populations. Additionally, the specific alleles of HLA-Cw*0602 and CDSN*5 consistently demonstrated a significant association with psoriasis (142,143). Tawfik *et al* (144) conducted a study that showed an association between psoriasis and three variants (rs10484554, rs887466 and rs1062470), within the *PSORS1* locus. These

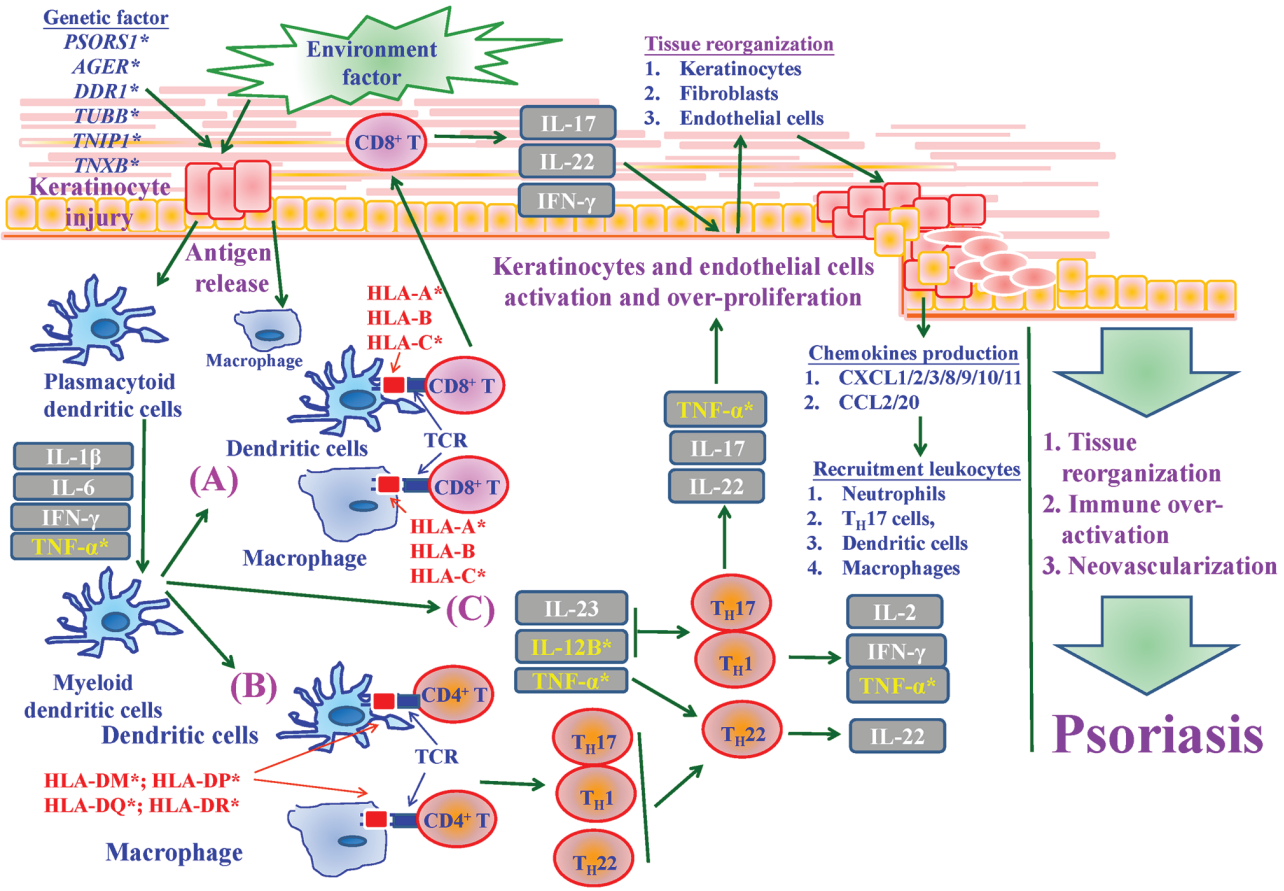


Figure 8. Molecular mechanisms involved in psoriasis are depicted. The damage to keratinocytes and the release of antigens are caused by genetic variables (*PSORS1, AGER, DDR1, TUBB, TNIP1* and *TNXB*) and environmental factors. At point (A), $CD8^+$ T cells are activated by APCs such as macrophages and dendritic cells that present the antigen through HLA-A, HLA-B and HLA-C. At point (B), APCs deliver antigens to $CD4^+$ T cells through HLA-D, which stimulates the differentiation of $CD4^+$ T cells into Th17, Th1 and Th22 cells. IFN-γ, IL-17 and IL-22 are also secreted. At point (C), Myeloid dendritic cells release the cytokines IL-23, IL-12B and TNF-α, which stimulate the growth of Th17, Th1 and Th22 cells. The cells also secrete IL-17, IL-22 and IFN-γ. As a result of the aforementioned findings, keratinocytes and endothelial cells are activated and grow excessively. In psoriasis, tissues are reconfigured, chemokines are produced, the immune system is over-activated, vascular proliferation occurs and neovascularization occurs. PSORS1, psoriasis susceptibility 1; AGER, advanced glycosylation end-product specific receptor; DDR1, discoidin domain receptor tyrosine kinase 1; TUBB, tubulin β class I; TNIP1, TNFAIP3 interacting protein 1; TNXB, tenascin XB; APCs, antigen-presenting cells; HLA-A, major histocompatibility complex, class I, A; HLA-B, major histocompatibility complex, class I, B; HLA-C, major histocompatibility complex, class I, C; HLA-D, major histocompatibility complex, class II, D; Th17 cells, T helper 17 cells; Th1 cells, T helper 1 cells; Th22 cells, T helper 22 cells; IFN-γ, Interferon γ; IL-17, interleukin 17; IL-12, interleukin 12; IL-12B, interleukin 12B; IL-22, interleukin 22; IL-23, interleukin 23; TNF, tumor necrosis factor.

variants are associated with *LOC105375015*, *PSORS1C3* and *PSORS1C1* (137). Additionally, GWAS identified 36 regions that contributed to psoriasis susceptibility. However, >50% of the genetic variance is attributed to a single *MHC* locus, specifically *PSORS1* (145). One of the candidate genes in psoriasis is *HLA-C*, as demonstrated by a GWAS performed using markers linked to *HLA-Cw*0602* (145). However, some studies have suggested that *PSORS1* does not play a role in the development of late-onset psoriasis (143,146,147). In the present study, a connection between psoriasis and specific genetic markers was discovered, namely, *PSORS1C1*, *PSORS1C2*, *PSORS1C3*, *MICA* and *CDSN*. These genes have been linked to various factors, such as human keratinocyte differentiation (53,148-150), the inflammatory response (112,151-153) and in medication toxicity, particularly the Stevens-Johnson syndrome associated with allopurinol (142,154,155).

In Taiwan, few studies have been conducted on the use of PRS for the treatment of psoriasis. Evidence suggests that diabetes mellitus is increasingly prevalent among patients with psoriasis (22,156,157). Eiris *et al* (158) showed a significant association between three SNPs (rs6887695, rs3212227 and rs2201841) and diabetes mellitus. Recent GWAS findings have indicated a genetic association between psoriasis and autoimmune diseases (such as multiple sclerosis, rheumatoid arthritis and autoimmune hypothyroidism), neuromuscular diseases (including Alzheimer's and Parkinson's diseases) (159-162), chronic inflammation (163) and skin diseases (164). Future investigations will aim to conduct a transdisease meta-analysis and Mendelian randomization to determine the causal relationship between psoriasis and the aforementioned diseases. It is important to note that the present study was subject to numerous limitations, including the risk of false positives and false negatives. It cannot be confirmed whether participants in the present were diagnosed with psoriasis or other autoimmune diseases at different hospitals, leading to such limitations in the present study. Additionally, due to the reliance on retrospective medical record reviews for selecting the experimental and control groups, accurate classification of the severity of

psoriasis could not be performed. It is also hypothesized that the severity of psoriasis is highly associated with genetics. Therefore, incorporating severity into future studies will likely significantly enhance the efficacy of the PRS model.

In conclusion, the present study has made significant discoveries regarding psoriasis in Taiwan. This confirms the influence of genetic variation and susceptibility on the development of psoriasis. Loci such as the HLA region, PSORS1 and IL-12B were identified that are strongly associated with psoriasis. The findings also showed an association between specific alleles, such as HLA-A*02:07 and HLA-C*06:02, and HLA genotypes, highlighting the role of genetic factors. Analysis of the PRS indicates that the location of SNPs can accurately predict psoriasis occurrence. Fig. 8 shows the importance of pathological mechanisms and signaling pathways in psoriasis development, as shown by the GWAS results of the present study. Importantly, the present study is the first to link multiple genetic loci in Taiwanese individuals with the onset of psoriasis. Overall, the present research emphasizes the critical role of genetic factors and signaling pathways in psoriasis development, providing valuable insights for future investigations and potential therapeutic interventions.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article. The data generated in the present study may be found at the following URL: https://my.locuszoom.org/gwas/590520/?token=2ea84c806f5f46aea3dcb3fb1ad21f99.

Authors' contributions

JSY, TYL and FJT were responsible for the overall conception and design. JSY, TYL and HFL performed the acquisition of data. TYL, JSY and YWW performed the GWAS, PRS and PheWAS analyses. TYL, HFL and WLL performed the interpretation of GWAS, PRS and PheWAS results. SCT, JSY and YJC performed the analysis of the bioinformatics network and interpreted the data. TYL and WLL assessed the HLA diplotypes, and performed the allele frequency analysis and interpretation of data. HFL and YWW performed the meta-analysis and interpretation of data. YJC and WLL performed the interpretation of clinical pathological mechanisms. JSY and FJT confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and informed consent

The study protocol was approved by the Institutional Review Board of China Medical University Hospital and categorized as the Precision Medicine Project (CMUHPMP) (IRB number: CMUH110-REC3-005 and CMUH111-REC1-176). Patients have been granted access to their medical records by the CMUH IRB. The CMUH IRB also places considerable emphasis on ensuring patient confidentiality. De-identified genetic and clinical data were collected after obtaining informed consent from patients. The present study complied with The Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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