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A genome-wide association study identifying key susceptibility loci for psoriasis: A genetic perspective

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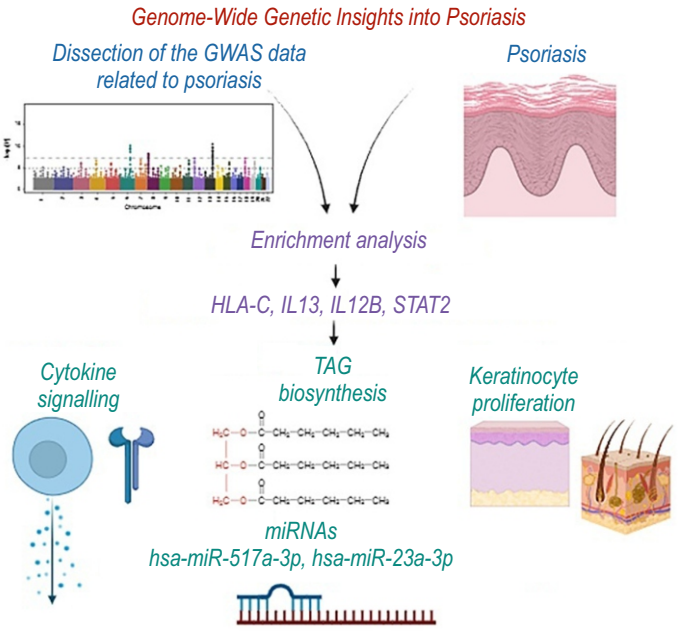
Abstract

Aim: To identify and functionally characterise key genetic susceptibility loci for psoriasis using GWAS data integrated with pathway, network, and regulatory analyses.

Methodology: GWAS datasets were systematically analysed to identify genes and genetic variants associated with psoriasis. Functional enrichment analyses were performed to delineate key biological pathways, regulatory elements, and functional annotations. Furthermore, transcription factor and microRNA interactions with psoriasis-related genes were evaluated to provide mechanistic insights.

Results: Multiple genetic loci were identified, reaffirming the contribution of immune dysregulation and impaired skin barrier function in psoriasis. Functional enrichment highlighted significant pathways including cytokine signalling, NF-κB activation, and keratinocyte proliferation. Several transcription factors and miRNAs regulating psoriasis-associated genes were also identified, offering additional layers of gene expression control.

Interpretation: Integration of GWAS findings with pathway and regulatory network analyses enhances the understanding of psoriasis genetics. Novel susceptibility genes, transcriptional regulators, and potential biomarkers have been identified, which may serve as therapeutic targets. Future research should focus on experimental validation and clinical translation to advance precision medicine approaches in psoriasis management.



Key words: Genetic susceptibility, GWAS Psoriasis, Immune-related loci, Inflammatory skin disease, Psoriasis genetics

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory disorder of the skin characterized by erythematous, scaly plaques, in which dysregulated keratinocyte differentiation and inflammation each contribute to disease pathology (Orzan *et al.,* 2025). The condition arises from an inappropriate immune response to unidentified autoantigens or microbial triggers, and is sustained by the recruitment and activation of leukocytes at the sites of developing lesions (Zhang *et al.,* 2024). Inflammatory cytokines, T cells, and dendritic cells are key drivers of this process (Zhang *et al.,* 2023). A strong genetic component has long been recognized: twin studies in Northern European populations show concordance rates of roughly 72 % in monozygotic twins compared with 15 – 23 % in dizygotic twins, with heritability estimates ranging from 60 – 90 %, underscoring a substantial genetic contribution to susceptibility (Dand *et al.,* 2025). Associations with major histocompatibility complex (MHC) haplotypes—especially HLA-Cw6—and single nucleotide polymorphisms (SNPs) near IL12B and IL23R further highlight genetic risk factors. Variants in these loci have also been implicated in other immune-mediated diseases such as Crohn's disease and ulcerative colitis (Ogawa and Okada, 2020).

Genome-wide association studies (GWAS) over the past decade have sought to uncover additional genetic determinants of psoriasis (Dand *et al.,* 2025). While these large-scale studies have produced incremental insights, they have successfully identified SNPs significantly linked to psoriasis risk, albeit often without a clear understanding of their functional roles (Dand *et al.,* 2020). Early GWAS efforts, including the landmark study by Nair *et al.* (2009), revealed psoriasis-associated loci within the NF-κB and IL-23 pathways, providing critical leads for subsequent research. Building on this foundation, the present study leverages mapped gene data from the GWAS Catalogue to investigate the biological significance of these genetic variants (Nair *et al.,* 2009). By integrating functional enrichment approaches—such as Gene Ontology (GO) classification, KEGG and Reactome pathway analyses, protein–protein interaction (PPI) network construction, microRNA (miRNA) enrichment using resources like TargetScan or miRTarBase, and metabolomic associations via Metabo Analyst—this work aimed to move beyond statistical correlation. The overarching goal was to clarify how GWAS-identified genes contribute to psoriasis pathogenesis, uncover regulatory mechanisms, and identify potential biomarkers for early diagnosis and disease prediction.

Materials and Methods

A comprehensive multi-step bioinformatics strategy was applied to elucidate the genetic and molecular pathways underlying psoriasis. Genome-wide association study (GWAS) data were first retrieved from the GWAS Catalogue to identify genes significantly associated with psoriasis (Sollis *et al.,* 2023). Variants meeting stringent statistical cutoffs and quality-control criteria, and with established clinical relevance, were selected. Mapped genes were retained for downstream analyses. Functional classification of the curated gene set was performed using Gene Ontology (GO) analysis to categorize genes into biological processes, molecular functions, and cellular components (Kuleshov *et al.,* 2016). Pathway enrichment was further investigated through the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa *et al.,* 2017) and Reactome databases (Croft *et al.,* 2011). To explore post-transcriptional and epigenetic regulation, microRNA (miRNA) enrichment analysis was performed using miRTarBase (Cui *et al.,* 2024) and TargetScan (Min and Yoon, 2010), thereafter, Protein–protein interaction (PPI) network analysis was conducted to uncover functional relationships among the psoriasis-associated genes. Network construction identified hub genes and closely interacting proteins that may act as key contributors to disease mechanisms.Finally, metabolomic relevance was evaluated with MetaboAnalyst to examine whether the mapped genes intersect with metabolic pathways implicated in psoriasis.

Results and Discussion

Genome-wide analysis identified multiple psoriasis-associated genomic regions and chromosomal loci (Table 1). Strong susceptibility loci include *HLA-C* (6p21.33), validating its role in immune-mediated inflammation, along with *TNFAIP3, STAT2, IL23R* and *IL12B*, all implicated in inflammatory and immunomodulatory pathways. The identification of HLA-C at 6p21.33 is consistent with earlier reports linking this locus to antigen presentation and immune cell recognition, both of which are central to the autoimmune cascade in psoriasis (Al Naqbi *et al.,* 2021). The co-identification of IL23R and IL12B in this analysis further validates the IL-23/IL-12 axis as a primary genetic driver, since these cytokine receptor and ligand genes together orchestrate the differentiation of Th17 cells, which are widely regarded as the principal effectors of psoriatic inflammation (Guo *et al.,* 2023). The presence of TNFAIP3 and STAT2 alongside these classical loci suggests that NF-κB regulation and interferon signalling also contribute independently to genetic susceptibility, pointing to a multi-pathway model of disease initiation rather than a single dominant mechanism (Jiang *et al.,* 2020).

MicroRNA enrichment (Table 2) revealed significant correlations between specific miRNAs and psoriasis-related genes in the GWAS Catalog. Notably, hsa-miR-451a is linked to *TSC1,* and hsa-miR-517a-3p shows the strongest association with *TNIP1*. Other key regulators include hsa-miR-23a-3p, hsa-miR-125a-5p and hsa-let-7i-5p, which target *TNFAIP3, STAT2* and *IL13*. The targeting of TNIP1 by hsa-miR-517a-3p is particularly relevant because TNIP1 is a negative regulator of Toll-like receptor and NF-κB signalling, and its suppression by this miRNA would be expected to amplify inflammatory signalling in keratinocytes (Li *et al.,* 2023). Similarly, the regulation of TNFAIP3 and STAT2 by hsa-miR-23a-3p and hsa-miR-125a-5p, respectively, suggests that post-transcriptional mechanisms may fine-tune the activity of key immune regulators in psoriatic skin, providing a layer of control beyond genetic variation at DNA level.

Table 1: GWAS findings of psoriasis

REGION	CHR_ID	CHR_POS	REPORTED GENE(S)	MAPPED_GENE
6p21.33	6	31,285,148	HLA-C	*RPL3P2 - WASF5P*
5q33.1	5	151,000,000	TNIP1	*TNIP1 - ANXA6*
1p31.3	1	67,228,519	IL23R	*C1orf141, IL23R*
5q31.1	5	133,000,000	IL13	*TH2LCRR, IL13*
5q33.3	5	159,000,000	IL12B	*UBLCP1 - IL12B*
12q13.3	12	56,344,189	STAT2, IL23A	*STAT2*
9q34.13	9	133,000,000	TSC1	*TSC1*
6q23.3	6	138,000,000	TNFAIP3	*TNFAIP3*

Table 2: miRTarBase 2017

Term	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
hsa-miR-517a-3p	p<0.05	0.227687	138.7153	662.6705253	*TNIP1*
hsa-miR-23a-3p	p<0.05	0.227687	14.53073	65.53122988	*TNFAIP3;TSC1*
hsa-miR-125a-5p	p<0.05	0.227687	13.47984	58.89925146	*STAT2;TNFAIP3*
hsa-let-7i-5p	p<0.05	0.227687	10.76396	42.54480225	*STAT2;IL13*
hsa-miR-451a	p<0.05	0.227687	55.43611	216.9520847	*TSC1*

The association of hsa-miR-451a with TSC1 connects miRNA regulation to mTOR pathway, which governs keratinocyte proliferation and is increasingly recognised as a therapeutic target in psoriasis (Joo *et al.,* 2024).

Reactome pathway analysis (Table 3) showed highest enrichment in Interleukin-12 family and Interleukin-23 signaling (P = 1.40E-05, OR = 518.96). Cytokine and interleukin pathways (IL-4, IL-13, IL-18, IFN) plus deubiquitination routes (*TNIP1, TNFAIP3*) highlight immune modulation. The strong enrichment of IL-23 signalling with an odds ratio of 518.96 is biologically consistent with the well-established centrality of the IL-23/Th17 axis in psoriasis pathogenesis (Bugaut and Aractingi, 2021). IL-23 drives the expansion and maintenance of Th17 cells, which in turn produce IL-17A, a cytokine that directly stimulates keratinocyte hyperproliferation and the recruitment of neutrophils to the skin. The enrichment of IL-4 and IL-13 signalling alongside IL-23 indicates that psoriasis involves a broader cytokine network than the Th17 axis alone, with Th2-related pathways also contributing, particularly in atopic comorbidities (Bridgewood *et al.,* 2021). The identification of ovarian tumour domain proteases through TNIP1 and TNFAIP3 is noteworthy, as these deubiquitinase enzymes regulate inflammatory signalling by removing ubiquitin chains from key immune regulators, and their dysregulation can sustain chronic NF-κB activation in psoriatic lesions (He *et al.,* 2025).

KEGG analysis identified the JAK-STAT pathway as most enriched (P = 2.80E-06, OR = 55.78) with links to chronic inflammatory disease (inflammatory bowel disease, P = 9.15E-06, OR = 96.41), IL-17 signaling, Th1/Th2 differentiation, viral infection, and cancer pathways. Key genes include *TNFAIP3, TSC1, IL23R, STAT2, Il13* and *IL12B*. The JAK-STAT pathway emerged as the most significantly enriched KEGG pathway, which is clinically meaningful given that JAK inhibitors are now approved treatments for psoriasis (Wang *et al.,* 2025). The enrichment of inflammatory bowel disease pathways alongside psoriasis-associated genes reflects the well-documented comorbidity between these conditions and suggests shared genetic architecture at the level of innate immune regulation (Grech *et al.,* 2025). The appearance of viral infection pathways in this analysis, driven partly by STAT2, points to the involvement of antiviral interferon responses in psoriasis, which aligns with the known triggering of psoriatic flares by viral infections and with the role of type I interferon signalling in sustaining chronic skin inflammation (Orzan *et al.,* 2025).

Protein-protein interaction (PPI) analysis (Table 4) highlighted JAK1 and JAK2 (P < 0.005, OR = 22.96–26.94) as central to JAK-STAT signaling. *UBC* links to *TNIP1, TNFAIP3* and *TSC1* (P = 0.0046, OR = 10.86), while *IKBKB* and *IKBKG* (P < 0.02, OR = 10.83–21.57) regulate NF-κB signaling. YWHA family proteins (YWHAE, YWHAG, YWHAZ, YWHAH) and ACTB (P = 0.019, OR = 10.60) indicate roles in signaling and cytoskeletal integrity. The centrality of JAK1 and JAK2 in the PPI network, interacting with both IL23R and STAT2, reflects their role as primary kinases that transduce cytokine receptor signals into transcriptional changes in immune cells (Vázquez-Jiménez *et al.,* 2025). Pharmacological inhibition of these kinases with small molecules has already demonstrated clinical efficacy in psoriasis, and their identification here as network hubs from an unbiased GWAS-based analysis independently validates this therapeutic rationale. The hub role of UBC, which interacts with TNIP1, TNFAIP3 and TSC1, underlines the importance of ubiquitin-

Table 3: Reactome Pathways 2024

Term	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
Interleukin-23 Signaling	p<0.05	7.70E-04	518.961	5800.000521	*IL23R;IL12B*
Interleukin-4 and Interleukin-13 Signaling	p<0.05	0.001291	54.71009	545.2835135	*IL23R;IL13;IL12B*
Signaling by Interleukins	p<0.05	0.00287	19.38393	169.8474918	*IL23R;STAT2; IL13;IL12B*
Ovarian Tumor Domain Proteases	p<0.05	0.00392	98.0344	800.2223504	*TNIP1;TNFAIP3*
Interleukin-12 Family Signaling	p<0.05	0.006477	67.11448	499.1544963	*IL23R;IL12B*

Table 4: PPI Hub Proteins

Term	Overlap	P-value	Adjusted P-value	Odds Ratio	Combined Score	Genes
JAK1	2/136	p<0.05	0.052417	26.93758	153.0437737	*IL23R;STAT2*
UBC	3/540	p<0.05	0.052417	10.86592	58.53914927	*TNIP1;TNFAIP3;TSC1*
JAK2	2/159	p<0.05	0.052417	22.96468	123.4644305	*IL23R;STAT2*
IKBKB	2/169	p<0.05	0.052417	21.57866	113.451394	*TNFAIP3;TSC1*
YWHAH	2/177	p<0.05	0.052417	20.5839	106.37205	*TNFAIP3;TSC1*

mediated protein degradation in controlling the magnitude of inflammatory responses, with dysregulation of this system contributing to sustained NF-κB activation characteristic of psoriatic plaques (Prema and Shanmugamprema, 2025).

Key molecular processes included viral defense (*IL23R, TNFAIP3, IL12B,* P = 1.65E-06, OR = 176.05), IL-10 synthesis regulation (*IL23R, IL13, IL12B,* P = 3.20E-06, OR = 139.14), NK/T-cell activation (P < 1.1E-05, OR = 605.48–1211.15), and cytokine signaling via JAK-STAT (P < 5.84E-06, OR = 908.31). The enrichment of viral defence processes driven by IL23R, TNFAIP3 and IL12B highlights an overlap between antiviral immunity and psoriasis-associated immune activation, suggesting that the genetic variants identified in GWAS may predispose individuals to heightened innate immune responses that, when triggered by microbial or environmental stimuli, tip into chronic inflammatory disease (Hamid, 2025). The strong enrichment of cytokine signalling via JAK-STAT with an odds ratio exceeding 900 reinforces the dominance of this pathway in psoriasis and is consistent with the broad therapeutic success of JAK inhibitors and biologics targeting the IL-23/IL-17 axis in clinical practice (Ożóg *et al.,* 2025).

Cellular localization showed *IL12B* and *ANXA6* in endosome lumen/late endosome (P<0.016, OR = 69.31–237.85), *TSC1* with actin filaments (P = 0.045, OR = 23.71) and lipid droplets (P = 0.052, OR = 20.47) and *IL12B* in the ER lumen (P = 0.169, OR = 5.80). The localisation of IL12B and ANXA6 to endosomal compartments is relevant to immune signalling, as endosomes serve as platforms for Toll-like receptor activation and cytokine receptor processing, and disruption of endosomal trafficking can alter the duration and intensity of inflammatory signalling. The association of TSC1 with actin filaments connect this gene to cytoskeletal regulation, which plays a role in immune cell migration and formation of immunological synapses, processes that are relevant to infiltration of T cells and dendritic cells into psoriatic skin lesions.

Molecular functions included cytokine receptor binding (*IL23R, IL12B,* P < 0.002, OR = 36.89–48.92), growth factor receptor binding (P = 0.0017, OR = 38.48), telomerase RNA binding by TNIP1 (P = 0.013, OR = 83.19), ubiquitination by *TNFAIP3* (P = 0.0084, OR = 138.71), and ANXA6 ion-gated channel activity (P = 0.025, OR = 42.62). Cytokine receptor binding by IL23R and IL12B is directly mechanistic in psoriasis, as these interactions initiate the signalling cascades that drive Th17 cell differentiation and sustain the inflammatory loop between keratinocytes and immune cells (Li *et al.,* 2025). The ubiquitination activity attributed to TNFAIP3 is also relevant here, since TNFAIP3 (A20) functions as a ubiquitin-editing enzyme that limits NF-κB activation by removing activating ubiquitin chains from signalling intermediates, and loss of this regulatory function is expected to amplify inflammatory responses in susceptible individuals (Orozco *et al.,* 2025).

Immune cell interactions revealed the roles in $CD4^+$ T-cell activation (P < 0.02, OR = 55.43–165), macrophage polarization (*IL12B, IL13,* P = 0.0038–0.0148), effector T cells (P = 0.0051, OR = 2378.5), MAIT cells (P = 0.0058, OR = 208.11), and Th2/eosinophil responses (*IL13,* P = 0.0077, OR = 151.33). The enrichment of CD4+ T-cell activation and effector T-cell categories is consistent with the established central role of adaptive immunity in psoriasis, where pathogenic T cells recognise self-antigens and sustain keratinocyte activation through cytokine release (Yao *et al.,* 2025). The identification of macrophage polarisation driven by IL12B and IL13 indicates that innate immune cells also contribute to disease heterogeneity, with IL-12 promoting pro-inflammatory M1 macrophage states and IL-

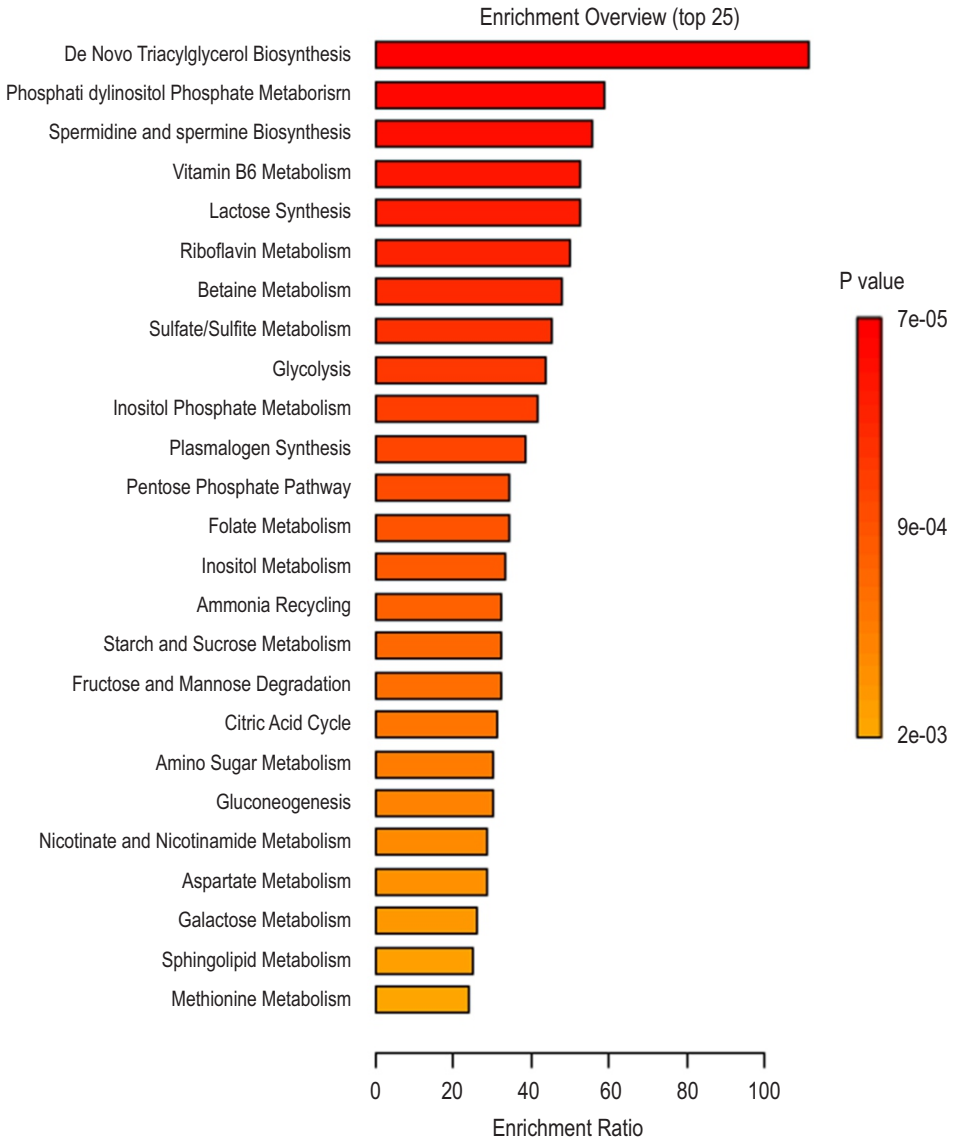

Fig. 1: Important pathways linked to lipid metabolism, amino acid metabolism, and energy production by ranking the top 25 enriched metabolic pathways by enrichment ratio. The color intensity indicates statistical significance (p-value).

13 associated with Th2-skewed responses that may characterise certain psoriasis subtypes or comorbid atopic phenotypes (Prados-Carmona *et al.,* 2025).

Metabolite analysis linked *UBLCP1* to phosphate (P = 0.193, OR = 5.01) and magnesium (P = 0.262, OR = 3.52), suggesting roles in energy metabolism and immune regulation. Although the associations of phosphate and magnesium with UBLCP1 did not reach formal statistical significance, they are biologically plausible given that magnesium is required as a cofactor for numerous kinases and phosphatases that regulate immune cell activation and cytokine production (Wu *et al.,* 2025). Phosphate homeostasis is similarly linked to energy metabolism through ATP synthesis, and immune cells undergoing rapid proliferation and cytokine secretion have substantially elevated metabolic demands that would be sensitive to perturbations in these essential ions. RNA-seq data showed downregulation of *TNIP1, TNFAIP3, ANXA6, STAT2, IL12B, Il13* and *IL23R* across multiple datasets implicating impaired NF-κB and interferon signaling. Conversely, these genes are consistently upregulated in other datasets, indicating activation of inflammatory and antiviral pathways. The bidirectional expression patterns of these genes across datasets likely reflect the heterogeneity of psoriasis, where disease stage, tissue site, and treatment history

can substantially alter the transcriptional state of lesional skin. The downregulation of TNIP1 and TNFAIP3 in some datasets is consistent with impaired negative regulation of NF-κB signalling, which would remove a brake on inflammatory gene expression and contribute to the sustained cytokine production seen in active psoriatic plaques (Li *et al.,* 2025). Conversely, their upregulation in other datasets may reflect compensatory induction of these regulatory genes in response to elevated inflammatory activity.

Metabolic pathway enrichment (Fig. 1) highlighted De Novo Triacylglycerol Biosynthesis as most significant, with additional enrichment in spermidine/spermine biosynthesis, phosphatidylinositol phosphate metabolism, glycolysis, citric acid cycle, gluconeogenesis, and vitamin B6/riboflavin metabolism, reflecting links to immune function, lipid homeostasis, and disease progression. The enrichment of de novo triacylglycerol biosynthesis as a top metabolic pathway is consistent with the lipid abnormalities that have been described in psoriatic skin, where altered lipid metabolism in keratinocytes contributes to impaired barrier function and facilitates immune cell infiltration (Tu *et al.,* 2025). The enrichment of glycolysis and citric acid cycle reflects high metabolic activity of proliferating keratinocytes and activated immune cells in psoriatic lesions, since rapidly dividing cells switch to aerobic glycolysis to meet their biosynthetic demands. Polyamine metabolism through spermidine and spermine biosynthesis has also been linked to keratinocyte proliferation, and its enrichment here suggests a metabolic contribution to the hyperproliferative epidermal phenotype that is characteristic of psoriatic plaques.

This study integrates GWAS, GO, pathway, miRNA enrichment, PPI network and metabolomics analyses to explain the genetic and molecular basis of psoriasis, providing insights consistent with prior research. Psoriasis showed strong associations with immune-regulatory genes *TNFAIP3, STAT2, IL23R, IL12B* and *HLA-C*, highlighting antigen presentation and immune response in disease etiology (Bojko *et al.,* 2018; Guo *et al.,* 2023). *IL23R* and *IL12B,* key to the IL-23/IL-12 pathway, support their role in Th17-driven inflammation (Girolomoni *et al.,* 2017). The addition of *TNFAIP3* and *STAT2* suggests NF-κB and interferon signaling involvement (Kim *et al.,* 2020).

The consistent identification of *HLA-C, IL23R, IL12B, TNFAIP3* and *STAT2* across multiple analytical platformed in this study strengthens their candidacy as core genetic determinants of psoriasis susceptibility, and the convergence of pathway, network, miRNA, and the metabolomic evidence around the IL-23/JAK-STAT/NF-κB regulatory axis provides a coherent mechanistic framework for how these loci translate genetic risk into disease. These findings collectively reinforce the multi-pathway nature of psoriasis and highlight potential targets for biologic and small-molecule therapeutic intervention (Shi *et al.,* 2025). Gene Ontology analysis revealed immune activation, cytokine signaling, and inflammatory modulation, with enrichment in JAK-STAT activation and IL-10 regulation (Cheemalavagu *et al.,* 2024). Molecular functions included cytokine receptor binding and ubiquitination (*TNFAIP3, TNIP1*) (Shamilov and Aneskievich, 2018). Cellular components such as endosomes and cytoskeleton further link immune regulation (Kaminska *et al.,* 2024). KEGG and Reactome enrichment confirmed IL-23/IL-12 and JAK-STAT pathways and highlighted viral infection and inflammatory bowel disease pathways. Deubiquitination and ovarian tumor domain proteases indicate post-translational immune regulation (Schlüter *et al.,* 2022). miRNA analysis identified hsa-miR-517a-3p targeting *TNIP1*; hsa-miR-23a-3p and hsa-miR-125a-5p targeting *TNFAIP3* and *STAT2;* hsa-let-7i-5p regulating *STAT2* and *IL13;* and hsa-miR-451a linked to *TSC1,* implicating keratinocyte proliferation (Peng *et al.,* 2022). These findings reveal therapeutic miRNA-mediated regulation. PPI analysis identified JAK1, JAK2, and UBC as hubs, with NF-κB regulators *IKBKB, IKBKG* and *TNFAIP3* central to immune activation (10). ACTB and YWHA proteins suggest broader roles in apoptosis and structure.

Metabolomic analysis implicated phosphate and magnesium in ATP synthesis, signal transduction, and immune enzyme activity, suggesting metabolic contributions despite modest significance (Fiorentini *et al.,* 2021). Overall, enrichment analyses link genetic variants to immunological and inflammatory pathways, closing the gap between GWAS findings and disease mechanisms. One of the limitations of the study is that metadata was not taken into consideration, which could have provided more valuable insights and a deeper understanding of the results.The enrichment analysis results should be interpreted as trends and approached with caution when drawing conclusions. This systems biology perspective suggests potential regulatory factors and therapeutic targets for precision medicine in psoriasis, though these findings require further validation.

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References

Al Naqbi, H., A. Mawart, J. Alshamsi, H. Al Safar and G.K. Tay: Major histocompatibility complex (MHC) associations with diseases in ethnic groups of the Arabian Peninsula. *Immunogenetics,* **73**, 131-152 (2021).

Bojko, A., R. Ostasz, M. Bialecka, A. Klimowicz, D. Malinowski, R. Budawski, P. Bojko, M. Drodzik and M. Kurzawski: IL12B, IL23A, IL23R and HLA-C*06 genetic variants in psoriasis susceptibility and response to treatment. *Hum. Immunol.,* **79**, 213-217 (2018).

Bridgewood, C., D. Newton, N. Bragazzi, M. Wittmann and D. McGonagle: Unexpected connections of the IL-23/IL-17 and IL-4/IL-13 cytokine axes in inflammatory arthritis and enthesitis. *Semin. Immunol.,* **58**, 101520 (2021).

Bugaut, H. and S. Aractingi: Major role of the IL17/23 axis in psoriasis supports the development of new targeted therapies. *Front. Immunol.,* **12**, 621956 (2021).

Cheemalavagu, N., K.E. Shoger, Y.M. Cao, B.A. Michalides, S.A. Botta, J.R. Faeder and R.A. Gottschalk: Predicting gene-level sensitivity to JAK-STAT signaling perturbation using a mechanistic-to-machine learning framework. *Cell Syst.,* **15**, 37-48 (2024).

Croft, D., G. O'Kelly, G. Wu, R. Haw, M. Gillespie, L. Matthews, M. Caudy, P. Garapati, G. Gopinath, B. Jassal, S. Jupe, I. Kalatskaya, S. Mahajan, B. May, N. Ndegwa, E. Schmidt, V. Shamovsky, C. Yung, E. Birney, H. Hermjakob, P. D'Eustachio and L. Stein: Reactome: a database of reactions, pathways and biological processes. *Nucl. Acids Res.,* **39**, D691-D697 (2011).

Cui, S., S. Yu, H.Y. Huang, Y.C.D. Lin, Y. Huang, B. Zhang, J. Xiao, H. Zuo, J. Wang, Z. Li, G. Li, J. Ma, B. Chen, H. Zhang, J. Fu, L. Wang and H.D. Huang: miRTarBase 2025: updates to the collection of experimentally validated microRNA-target interactions. *Nucl. Acids Res.,* **53**, D147-D156 (2024).

Dand, N., S.K. Mahil, F. Capon, C.H. Smith, M.A. Simpson and J.N. Barker: Psoriasis and genetics. *Acta Derm. Venereol.,* **100**, adv00030 (2020).

Dand, N., P.E. Stuart, J. Bowes, D. Ellinghaus, J. Nititham, J.R. Saklatvala, M. Teder-Laving, L.C. Tsoi, T. Opsahl-Dreyer, T. Rognstad, O. Nyman, J. Hveem, K. Hveem, J. Mucha, H. Schreiber, R. Bergboer, E. Gnarra, M. Spindola, G. Kingo, K. Traks, C. Brück, A. Ellinghaus, J. Baurecht, M. Weidinger, A. Strange, M. Cobain, J. Barker, C. Smith, M. Simpson, M. Cordell, S. Cork and F. Capon [HIGHLIGHT: Nat. Commun. 2025;16:2051 — please verify complete author list at doi:10.1038/s41467-024-55094-6]: GWAS meta-analysis of psoriasis identifies new susceptibility alleles impacting disease mechanisms and therapeutic targets. *Nat. Commun.,* **16**, 2051 (2025).

Fiorentini, D., C. Cappadone, G. Farruggia and C. Prata: Magnesium: biochemistry, nutrition, detection, and social impact of diseases linked to its deficiency. *Nutrients,* **13**, 1136 (2021).

Girolomoni, G., R. Strohal, L. Puig, H. Bachelez, J. Barker, W.H. Boehncke and J.C. Prinz: The role of IL-23 and the IL-23/T(H) 17 immune axis in the pathogenesis and treatment of psoriasis. *J. Eur. Acad. Dermatol. Venereol.,* **31**, 1616-1626 (2017).

Grech, V.S., K. Lotsaris, V. Kefala and E. Rallis: From skin to brain: key genetic mediators associating cutaneous inflammation and neurodegenerative diseases. *Genes,* **16**, 1463 (2025).

Guo, J., H. Zhang, W. Lin, L. Lu, J. Su and X. Chen: Signaling pathways and targeted therapies for psoriasis. Signal Transduct. *Target. Ther.,* **8**, 437 (2023).

Hamid, N.: Unraveling the genetic landscape of psoriasis: a genome-wide association study in Egypt. *Sci. J. Dermatol. Venereol.,* **3**, 24-38 (2025).

He, Y., J. Xing, J. Li, K. Zhang and X. Li: S100A8 and S100A9-mediated keratinocyte affecting T lymphocyte immune imbalance through TLR4/NF-kB in psoriasis. *Acta. Histochem.,* **127**, 152297 (2025).

Jiang, Y., W. Wang, X. Zheng and H. Jin: Immune regulation of TNFAIP3 in psoriasis through its association with Th1 and Th17 cell differentiation and P38 activation. *J. Immunol. Res.,* **2020**, 5980190 (2020).

Joo, K., C. Karsulovic, M. Sore and L. Hojman: Pivotal role of MTOR in non-skin manifestations of psoriasis. *Int. J. Mol. Sci.,* **25**, 6778 (2024).

Kaminska, P., A. Tempes, E. Scholz and A.R. Malik: Cytokines on the way to secretion. *Cytok. Grow. Fac. Rev.,* **79**, 52-65 (2024).

Kanehisa, M., M. Furumichi, M. Tanabe, Y. Sato and K. Morishima: KEGG: new perspectives on genomes, pathways, diseases and drugs. *Nucl. Acids Res.,* **45**, D353-D361 (2017).

Kim, T., S.C. Bae and C. Kang: Synergistic activation of NF-kB by TNFAIP3 (A20) reduction and UBE2L3 (UBCH7) augment that synergistically elevate lupus risk. *Arthr. Res. Ther.,* **22**, 93 (2020).

Kuleshov, M.V., M.R. Jones, A.D. Rouillard, N.F. Fernandez, Q. Duan, Z. Wang, S. Koplev, S.L. Jenkins, K.M. Jagodnik, A. Lachmann, M.G. McDermott, C.D. Monteiro, G.W. Gundersen and A. Ma'ayan: Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. *Nucl. Acids Res.,* **44**, W90-W97 (2016).

Li, L., J. Liu, J. Lu, J. Wu, X. Zhang, T. Ma, X. Wu, J. Zheng, Z. Deng, Y. Sun, X. Wen, M. Wang, H. Chen, C. Sun, J. Zhao and J. Sun [HIGHLIGHT: Front. Immunol. 2025;16:1573905 — please verify complete author list]: Interventions in cytokine signaling: novel horizons for psoriasis treatment. *Front. Immunol.,* **16**, 1573905 (2025).

Li, L., J. Lu, J. Liu, J. Wu, X. Zhang, Y. Meng, X. Wu, J. Zheng, Z. Deng, Y. Sun, X. Wen, M. Wang, H. Chen, C. Sun, J. Zhao and J. Sun [HIGHLIGHT: Front. Immunol. 2023;14:1340677 — please verify complete author list]: Immune cells in the epithelial immune microenvironment of psoriasis: emerging therapeutic targets. *Front. Immunol.,* **14**, 1340677 (2023).

Min, H. and S. Yoon: Got target? Computational methods for microRNA target prediction and their extension. *Exp. Mol. Med.,* **42**, 233-244 (2010).

Nair, R.P., K.C. Duffin, C. Helms, J. Ding, P.E. Stuart, D. Goldgar, J.E. Gudjonsson, Y. Li, T. Tejasvi, B.J. Feng, A. Ruether, S. Schreiber, M. Weichenthal, D. Gladman, P. Rahman, S.J. Schrodi, S. Prahalad, S.L. Guthery, J. Fischer, W. Liao, P.Y. Kwok, A. Menter, G.M. Lathrop, C.A. Wise, A.B. Begovich, J.J. Voorhees, J.T. Elder, G.G. Krueger, A.M. Bowcock and G.R. Abecasis: Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat. Genet.,* **41**, 199-204 (2009).

Ogawa, K. and Y. Okada: The current landscape of psoriasis genetics in 2020. *J. Dermatol. Sci.,* **99**, 2-8 (2020).

Orozco, B.E., C.V. Orozco, E. Melendez, M.F. Mangones, J. Valderrama, A. Lobato, P. Garavito-Galofre, J.I. Velez and O.M. Vidal: Co-occurrence of RAD21 and TNFAIP3 mutations in Cornelia de Lange syndrome with pustular psoriasis: potential molecular interactions. *Int. J. Mol. Sci.,* **26**, 10783 (2025).

Orzan, O.A., C.V. Tutunaru and S.L. Ianosi: Understanding the intricate pathophysiology of psoriasis and related skin disorders. *Int. J. Mol. Sci.,* **26**, 749 (2025).

Ożóg, M.K., A. Derkacz, D. Klimczak, S. Winkler and L. Wojciuch: New

therapies in the biological treatment of psoriasis: a review. *Allergies,* **5**, 19 (2025).

Peng, Y.Y., H.B. Zhang, X. Wang, Q. Xiao and S.L. Guo: The biomarkers of key miRNAs and gene targets associated with extranodal NK/T-cell lymphoma. *Open Med.,* **17**, 124-134 (2022).

Prados-Carmona, A., H. Husein-ElAhmed, F.J. Navarro-Trivino and R. Ruiz-Villaverde: Atopic dermatitis beyond eczema: a review on its systemic impact through pruritus and associated comorbidities. *Clin. Rev. Allergy Immunol.,* **68**, 66 (2025).

Prema, S.S. and D. Shanmugamprema: Systemic psoriasis: from molecular mechanisms to global management strategies. *Clin. Rev. Aller. Immunol.,* **68**, 79 (2025).

Schlüter, D., E. Schulze-Niemand, M. Stein and M. Naumann: Ovarian tumor domain proteases in pathogen infection. *Trends Microbiol.,* **30**, 22-33 (2022).

Shamilov, R. and B.J. Aneskievich: TNIP1 in autoimmune diseases: regulation of toll-like receptor signaling. *J. Immunol. Res.,* **2018**, 3491269 (2018).

Shi, W., Z. Zhao, Y. Zhai, X. Ye and F. Xu: Adverse events associated with IL-23 and IL-12/23 inhibitors in the clinical management of psoriasis: a comprehensive pharmacovigilance analysis. *BMC Pharmacol. Toxicol.,* **26**, 11 (2025).

Sollis, E., A. Mosaku, A. Abid, A. Buniello, M. Cerezo, L. Gil, T. Groza, O. Güneş, P. Hall, J. Hayhurst, A. Ibrahim, Y. Ji, S. John, E. Lewis, J.A.L. MacArthur, A. McMahon, D. Osumi-Sutherland, K. Panoutsopoulou, Z. Pendlington, S. Ramachandran, R. Stefancsik, J. Stewart, P. Whetzel, R. Wilson, L. Hindorff, F. Cunningham, S.A. Lambert, M. Inouye, H. Parkinson and L.W. Harris: The NHGRI-EBI GWAS catalog: knowledgebase and deposition resource. *Nucl. Acids Res.,* **51**, D977-D985 (2023).

Tu, Y., H. Gu, N. Li, D. Sun, Z. Yang and L. He: Identification of key genes related to immune-lipid metabolism in skin barrier damage and analysis of immune infiltration. *Inflammation,* **48**, 2051-2068 (2025).

Vázquez-Jiménez, S.I., G.D. Gonzalez-Sanchez, C. Guerrero-Velazquez and J.M. Guzman-Flores: Interpreting the function of the IL-23/IL-17 axis through bioinformatics. *Endocr. Metab. Immune Disord. Drug. Targets,* **25**, 429-441 (2025).

Wang, C., Z. Liu, Y. He, Y. Zhang, S. Chen, Y. Zhou, W. Yang and L. Fan: Identification of novel biomarkers related to pathogenesis and treatment of psoriasis based on integrated analysis of weighted gene co-expression network analysis and LASSO. *PLoS ONE,* **20**, e0317666 (2025).

Wu, C.S., F.C. Liu, S.C. Lin and I.T. Chyuan: Regulation of T cell receptor (TCR) signaling by tyrosine phosphatases: recent advances and implication for therapeutic approach in autoimmune diseases. *J. Formos. Med. Assoc.,* S0929-6646(25)00192-5 (2025).

Yao, Y., L.Q. Chen, Y.B. Lv, S.L. Tang, W. Shen, H. Sun and H.J. Zhong: Skin immune microenvironment in psoriasis: from bench to bedside. *Front. Immunol.,* **16**, 1643418 (2025).

Zhang, F., Y. Xia, J. Su, F. Quan, H. Zhou, Q. Li, Q. Feng, C. Lin, D. Wang and Z. Jiang: Neutrophil diversity and function in health and disease. *Signal Transduct. Target. Ther.,* **9**, 343 (2024).

Zhang, P., Y. Su, S. Li, H. Chen, R. Wu and H. Wu: The roles of T cells in psoriasis. *Front. Immunol.,* **14**, 1081256 (2023).