

Identification of Psoriasis Key Genes through Machine Learning and Construction of Transcriptional Regulatory Networks

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Abstract:

Psoriasis is a chronic inflammatory skin disease with a complex interplay of genetics, immune system, and environmental factor. This study aimed to explore the molecular mechanisms of psoriasis and identify key genes through bioinformatics analysis of transcriptomic data. In this study, the Gene Expression Omnibus (GEO) database was utilized to integrate three gene expression datasets of psoriasis patients, data integration was performed using the Robust Rank Aggregation (RRA) algorithm, followed by gene selection employing protein-protein interaction network construction and the Random Forest algorithm. Subsequently, we employed the CIBERSORT algorithm to analyze immune cell infiltration characteristics, and correlation analysis was conducted to explore the association between key genes and differences in immune cell infiltration. Furthermore, we constructed transcription factor regulatory networks of key genes to delve into their roles in disease. This study identified 473 upregulated and 288 downregulated differentially expressed genes. Through the construction of a protein-protein interaction network and screening with the Random Forest algorithm, HERC6, SAMD9, SPRR2B, S100A7A, SERPINB4, PI3, and SERPINB3 were identified as key genes associated with psoriasis. These genes are likely involved in the modulation of the local tissue immune microenvironment. Further analysis of transcription factor regulatory networks indicated that they might be regulated by eight important transcription factors, including CUX1, STAT1, PAX4, STAT2, ELF3, E2F1, STAT3, and NFIL3. The study provides a foundational understanding for future investigations into disease mechanisms and therapeutic strategies.

Keywords:

Psoriasis, Gene Expression, Bioinformatics, Protein-Protein Interaction Network, Transcription Factor Regulatory Network

1. Introduction

Psoriasis is a prevalent chronic inflammatory dermatological condition characterized by hyperproliferation, aberrant epidermal keratinization, disrupted cell proliferation and differentiation, and inflammatory cell infiltration. Globally, psoriasis affects approximately 2% to 4% of the population, predominantly manifesting in adults. [1] Despite its considerable prevalence, the precise etiology of psoriasis remains incompletely elucidated, posited to arise from intricate interplays among the immune system, epidermal barrier, and environmental factors. While triggers such as streptococcal infections, pharmaceutical agents, and physical trauma can incite psoriatic episodes, [2] recent attention has turned towards unraveling the genetic determinants underlying susceptibility to psoriasis. [3,4] Epidemiological studies underscore psoriasis as a polygenic disorder, wherein multiple genes with modest effects interact with each other and environmental stimuli to confer individual predisposition to the disease. [5]

The hereditary nature of psoriasis plays a significant role in disease susceptibility. Environmental stimuli, including trauma, infection, exposure to certain medications, and high-stress conditions, are considered potential triggering factors for psoriasis, particularly in individuals with genetic predisposition. [6] The complex involvement of the immune system further complicates the understanding of the pathogenesis of psoriasis, as immune system dysregulation plays a central role in the initiation and progression of the disease.

In recent years, despite the availability of effective treatments for psoriasis, the disease is notorious for its frequent recurrence. Therefore, there is a need for in-depth research into its underlying molecular mechanisms to identify new therapeutic targets. The Gene Expression Omnibus (GEO) database serves as a vast and comprehensive public resource of gene expression data, encompassing data from various disease gene expression profiles. [7] This study utilized the Robust Rank Aggregation (RRA) algorithm to integrate three public microarray datasets, employing the Random Forest algorithm and protein-protein interaction network analysis to screen genes within the integrated dataset. Ultimately, we successfully identified seven key genes: HERC6, SAMD9, SPRR2B, S100A7A, SERPINB4, PI3, and SERPINB3. Furthermore, this study constructed a transcription factor regulatory network for the key genes. Through this research, we aim to provide innovative insights into the pathogenesis and treatment of psoriasis, contributing to the development of more effective therapeutic strategies.

2. Methodology

2.1. Data Source and Preprocessing

The Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>) was searched for datasets pertaining to psoriasis patients. The following search terms were utilized: Psoriasis OR Psoriasis vulgaris OR Plaque psoriasis OR Psoriatic dermatitis OR Psoriatic erythroderma OR Guttate psoriasis. Two researchers independently screened the database and selected datasets based on the following criteria: (1) Whole-genome gene expression or non-coding RNA high-throughput array sequencing datasets or next-generation sequencing datasets from psoriasis patients. (2) Samples derived from human skin tissue. (3) Data available for reanalysis, such as raw or processed data. (4) Datasets not meeting the

mentioned criteria were excluded. Following the screening process, three datasets, namely GSE30999, GSE50790, and GSE30999, were selected for analysis.

2.2. RRA (Robust Rank Aggregation) Analysis and Dataset Integration

Gene expression data were annotated using appropriate annotation packages and R software (version 4.1.0). Expression data were further standardized using the “limma” package. [8] Subsequently, RRA analysis was conducted using the “Robust Rank Aggregation” package to rank differentially expressed genes (DEGs) in terms of upregulation and downregulation. [9] For each gene in the final list, a score representing its ranking was calculated, and genes with scores less than 0.05 were selected as significant DEGs. Batch effects among the three gene sets were removed using the removeBatchEffect function to integrate the datasets for subsequent analysis.

2.3. Functional of Differentially Expressed Genes

To elucidate the biological functions of the identified DEGs, Gene Ontology Biological Process (GOBP) were performed using the Metascape tool. [10] Multiple testing-corrected p-values less than 0.05 were considered significant, and visualization tools provided by Metascape were utilized to illustrate the distribution of DEGs in these biological processes.

2.4. Construction of Protein-Protein Interaction Networks and Modular Analysis

2.4.1. PPI Network Construction

To explore the interactions among DEGs, a protein-protein interaction (PPI) network was constructed using the STRING database (<https://string-db.org/cgi/input.pl>). High-confidence protein interactions were selected, and the PPI network of DEGs was visualized using Cytoscape software (version 3.9.0).

2.4.2. Modular Analysis

Functional clustering modules with high interaction relevance were further identified using the MCODE plugin in Cytoscape. Parameters were set as follows: degree cut-off = 2, node score cut-off = 0.2, Max depth = 100, and k-score = 2. The two most tightly connected modules were identified as key modules.

2.5. Gene Selection Using Random Forest Algorithm

To identify key genes associated with psoriasis, the random forest (RF) algorithm was employed for variable selection. RF algorithm constructs multiple decision trees, each trained using different subsets of data and features. MeanDecreaseGini, a measure of variable importance, indicates the average decrease in the Gini index for each variable in each split. A threshold of MeanDecreaseGini > 4 was set for variable selection to exclude redundant variables.

2.6. Estimation of Immune Cell Proportions and Correlation with Hub Genes

Immune dysfunction is considered a crucial pathogenic mechanism in psoriasis, and the CIBERSORT algorithm was utilized to detect relative abundance of cell types in bulk RNA-seq and microarray data. CIBERSORT deconvolution analysis was performed using the integrated dataset to assess differences in immune cell infiltration in tissues. [11] A p-value < 0.05 was considered statistically significant. Boxplots were constructed using ggplot2 to visualize the proportions of each immune cell type.

Spearman correlation coefficients were calculated to evaluate the correlation between each hub gene and immune cell types, visualized in heatmap format.

2.7. Construction of Transcriptional Regulatory Networks

The iRegulon tool [12] was employed to reveal transcriptional regulation relationships of key genes. iRegulon is a powerful bioinformatics tool specifically designed to predict associations between transcription factors (TFs) and target genes, and to construct transcriptional regulatory networks. Key parameters included: species and gene naming = “Homo sapiens, HGNC symbols”, motif collection = “10K (9713 PWMs)”, track collection = “1120 ChIP-seq tracks (ENCODE raw signals)”, potential regulatory regions = “20kb centered on TSS”, enrichment score threshold = 3.0, ROC threshold for AUC calculation = 0.03, and ranking threshold = 5000.

3. Results

3.1. Psoriasis Microarray Data

Following the filtration of GEO based on eligibility criteria, three microarray datasets related to psoriasis were ultimately selected. Information regarding these datasets, including researchers, RNA source types, GEO accession IDs, detection platforms, experimental types, and sample details, is listed. In total, 93 psoriatic lesion tissue samples and 93 normal skin tissue samples were included in this study analysis (Table 1)

Table 1. Sources and Characteristics of Included GEO Datasets.

GEO accession	Platform	Origin	Sample		Species	Type
			Control	Disease		
GSE166388	GPL570	Skin	4	4	Homo Sapiens	Microarray
GSE50790	GPL570	Skin	4	4	Homo Sapiens	Microarray
GSE30999	GPL570	Skin	85	85	Homo Sapiens	Microarray

3.2. Differential Expression Analysis Using Robust Rank Aggregation (RRA)

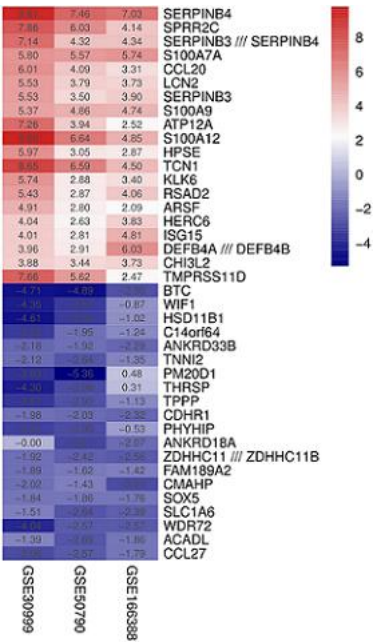


Figure 1. Heatmap of the top 20 upregulated and downregulated differentially expressed genes identified by the RRA algorithm.

By using the RRA method, we integrated three gene expression datasets and identified 473 upregulated and 288 downregulated differentially expressed genes (DEGs). The top 20 upregulated and downregulated mRNAs are shown in Figure 1.

3.3. Functional Enrichment Analysis of DEGs

To elucidate the underlying biological pathways associated with psoriasis, a comprehensive Gene Ontology (GO) enrichment analysis of all DEGs was conducted using Metascape (Figure 2). This analysis revealed that upregulated DEGs were notably enriched in innate immune response, bacterial response, cell cycle regulation, and inflammatory response pathways. Conversely, downregulated DEGs were predominantly associated with synaptic assembly regulation, fatty acid metabolism, and cellular component morphology pathways.

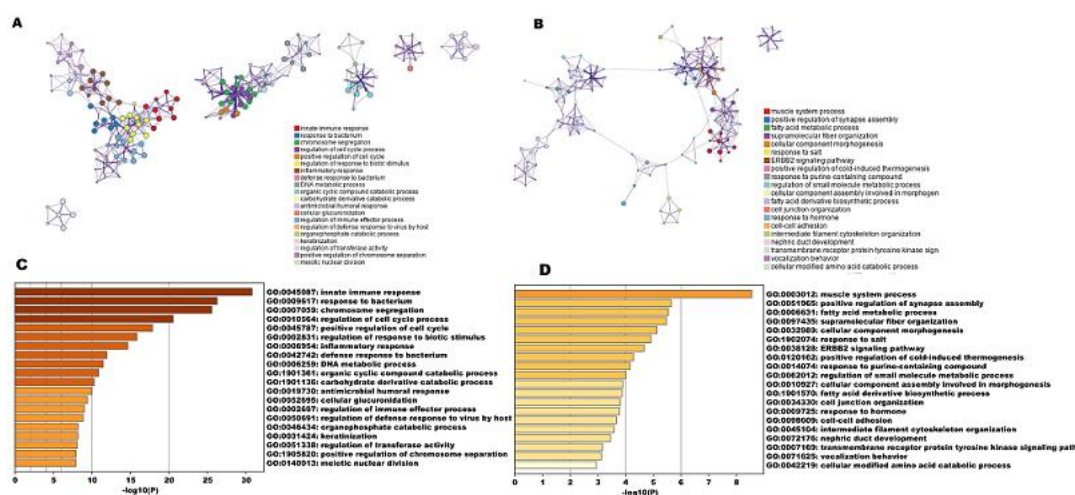
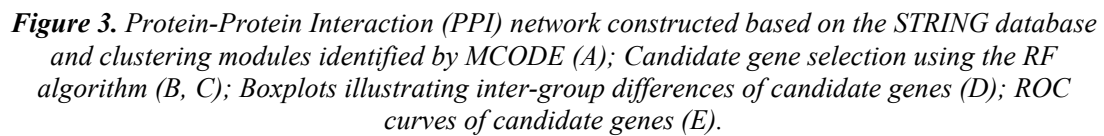


Figure 2. Enrichment functional analysis of upregulated (A, C) and downregulated (B, D) DEGs conducted through “Metascape”.

3.4. Construction of Protein-Protein Interaction (PPI) Network and Identification of Hub Genes

Subsequently, the Protein-Protein Interaction (PPI) network for these DEGs was established utilizing the STRING database (<https://string-db.org/>). Visualization was conducted using Cytoscape 3.90 software, followed by module clustering analysis employing the MCODE plugin. The top two densely interconnected modules comprised MKI67, CCNB1, PARP9, KIF2C, NEK2, BUB1, AURKA, NCAPH, IFI6, HMMR, CKS2, HERC6, DLGAP5, PBK, RTP4, RSAD2, TOP2A, TTK, SAMD9, ISG15, CEP55, HELZ2, IFIT3, KIF20A, IFI44L, KIF23, GBP1, EPSTI1, MELK, UBE2T, PLSCR1, IFIT1, RRM2, OAS3, MX1, SPC25, KIF4A, USP18, IRF7, CMPK2, DEPDC1B, CDKN3, CCNB2, OAS1, MCM10 (Cluster 1), and SPRR2B, S100A7A, SERPINB4, PI3, SERPINB3 (Cluster 2) (Figure 3A). Subsequently, we used random forest (RF) analysis for candidate gene selection (Figure 3B, 3C), resulting in the identification of seven candidate genes (HERC6, SAMD9, SPRR2B, S100A7A, SERPINB4, PI3, SERPINB3) with MeanDecreaseGini > 4 (Figure 3D). Their discerning capability between psoriatic and normal skin lesions is shown in Figure 3E.



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regulatory T cells compared to the control group ($p < 0.05$) (Figure 4A, 4B). Spearman correlation analysis was conducted to explore the relationship between hub genes and immune cells, revealing positive correlations between six hub genes (HERC6, SAMD9, SPRR2B, S100A7A, SERPINB4, PI3) and M1 macrophages and activated dendritic cells, while five genes (HERC6, SAMD9, SPRR2B, S100A7A, SERPINB4) exhibited negative correlations with regulatory T cells ($p < 0.05$) (Figure 4C).

3.6. Transcription Factor Regulatory Networks

Regulon is a computational method that utilizes cis-regulatory sequence analysis to infer transcriptional regulatory networks behind gene sets. This method employs genome-wide ranking and recovery approaches to detect enriched transcription factor motifs and their optimal sets of direct target genes. In this study, we employed iRegulon to predict the transcription factors (TFs) regulating hub genes and subsequently validated their expression levels in the microarray dataset. Our investigation revealed that hub genes are regulated by 18 transcription factors, with eight transcription factors exhibiting increased expression in psoriatic lesions, namely: CUX1, STAT1, PAX4, STAT2, ELF3, E2F1, STAT3, NFIL3. The regulatory network between these transcription factors and hub genes is depicted in Figure 5.

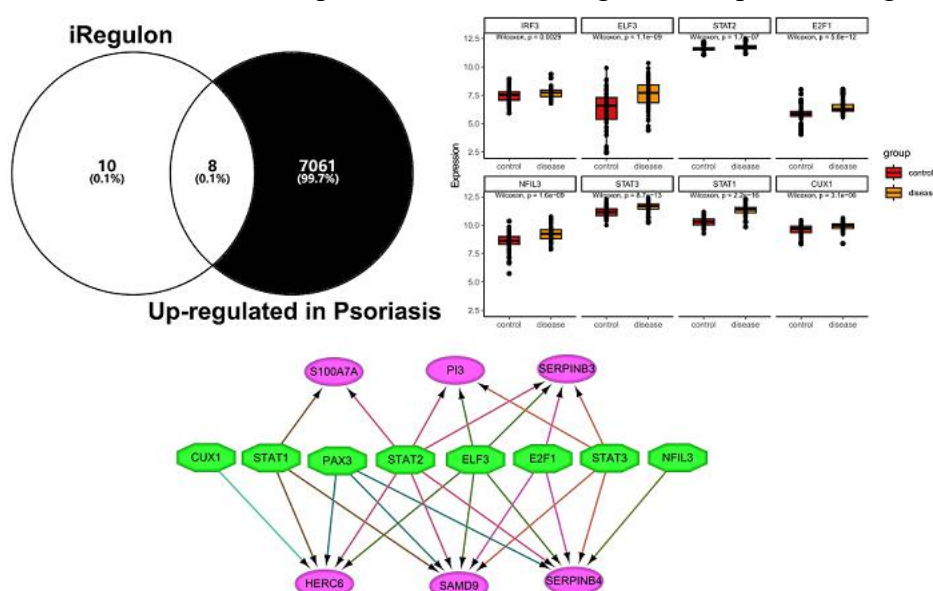


Figure 5. Transcriptional regulatory network construction of candidate genes.

4. Discussion

Our study conducted comprehensive bioinformatics analysis of psoriasis-associated genes by integrating data from three microarray databases and employing machine learning-based screening algorithms. Through this approach, we identified seven candidate genes: HERC6, SAMD9, SPRR2B, S100A7A, SERPINB4, PI3, and SERPINB3. Additionally, we conducted integrated analyses of the transcriptional regulatory networks of these candidate genes and their correlation with immune cell infiltration characteristics. This study provides a basis for the development of novel biomarkers and the exploration of the pathogenic mechanisms underlying psoriasis.

In the cohort of six hub genes, HERC6 ranks first. HERC6 belongs to the HECT and RCC1-like domain (RLD) family of ubiquitin ligase genes. Previous studies have

linked HERC6 to autoimmune diseases, antiviral processes, and interferon response. [13,14] For instance, in peripheral blood mononuclear cells of systemic lupus erythematosus (SLE) patients, HERC6 is upregulated and may promote disease progression through the JAK/STAT pathway. Consistent with previous omics analyses, our study found that HERC6 expression is upregulated in psoriatic lesions. [15,16] Moreover, our research underscores the correlation between HERC6 and immune cell infiltration and immune response. Recent studies suggest that the post-translational modification activity of HERC may contribute to the activation of NLRP3, which plays a crucial role in psoriasis and other autoimmune skin diseases. [17] Therefore, further investigation is warranted into the inflammation regulatory function of HERC6 in psoriasis.

The second gene of interest is SAMD9, also known as Sterile alpha motif domain-containing protein 9. This gene is implicated in various biological pathways, with previous research linking SAMD9 gene mutations to multisystem disorders, autoimmune diseases, and cancer. [18] Transcriptomic data indicate upregulation of SAMD9 in psoriasis, consistent with our study findings. Additionally, we note the association between SAMD9 and inflammatory response in disease. Genome-wide association analysis has revealed that missense mutations in SAMD9 correlate with the prognosis of sepsis patients, suggesting its crucial role in inflammatory responses involved in tissue damage and apoptosis. [19,20] Signal transducers and activators of transcription 2 (STAT2) and 3 (STAT3) participate in psoriasis-associated signaling pathways, playing essential roles in regulating immune responses and inflammation. Our study also reveals that the transcription factor STAT3 positively regulates SAMD9 expression. STAT3 is excessively activated in various cell types involved in psoriasis, including keratinocytes and Th17 cells, closely associated with disease progression. [21] Inhibiting its function may serve as a potential strategy for psoriasis treatment. SAMD9, as a crucial downstream target of STAT3, requires further investigation to elucidate its role in psoriasis.

From a pathological perspective, psoriatic skin exhibits features of abnormal differentiation in the upper epidermal layer (excessive keratinization, incomplete keratinization) [22] and inflammation (neutrophil infiltration in the epidermis, T cell infiltration in the dermis, and dermal vasodilation). [23] SPRR2B encodes a small protein rich in proline, serving as a cross-bridging protein of cornified envelopes, thus contributing to the main barrier function of the skin. Previous research has indicated elevated expression of SPRR proteins in psoriatic lesions, and their neighboring susceptible regions are causally linked to psoriasis. [24] However, the precise mechanism of action remains incompletely understood.

In the development of psoriasis, numerous cytokines and inflammatory regulatory factors also play significant roles. Studies have shown that skin-infiltrating T helper cells (Th1, Th17, and Th22 lymphocytes) participate in the disease process by releasing pro-inflammatory cytokines such as IL-17A, IL-22, TNF- α , and interferon-gamma. [25] These cytokines can upregulate the activity of the PI3K/AKT/mTOR pathway, leading to proliferation of keratinocytes and impairment of their differentiation, [26] which is consistent with the significant overexpression of the PI3 pathway. The upregulation of PI3 is significantly correlated with the infiltration of pro-inflammatory cells, and we also found significant upregulation of PI3 in psoriasis samples. SERPINB4 and SERPINB3 are also associated with inflammation. Research has shown that SERPINB4 promotes inflammation in keratinocytes through the p38MAPK signaling pathway, while the overexpression of SERPINB3 and its

protease degradation product Pso p27 is associated with early inflammation and barrier dysfunction in psoriasis. [27] Our study's findings of upregulation of SERPINB4 and SERPINB3 in psoriasis samples are consistent with previous research, indicating their potential role in dysregulation of skin homeostasis and the pathogenesis of psoriasis. Additionally, S100A7A, as a member of the S100 protein family, is induced by inflammatory stimuli and promotes the occurrence and development of psoriasis by influencing keratinocyte differentiation. [29] Its role in the disease makes it a potential target for therapeutic intervention and a candidate biomarker for diagnosis, as abnormal expression is associated with poor prognosis in psoriasis.

In addition to cytokines and inflammatory factors, abnormal activation and dysfunction of immune cells also play a crucial role in the development of psoriasis. For instance, CD8⁺ T cells significantly increase in psoriatic lesions and participate in inflammation and keratinocyte damage. Dendritic cells play a key role in immune responses. In psoriasis, they are abnormally activated and drive lesion formation by promoting T cell activation and release of inflammatory mediators. [30]

Overall, psoriasis is a complex disease involving dysregulation of various cytokines, inflammatory regulatory factors, and immune cell activation. The results of this study reveal multiple molecular pathways and immunological mechanisms involved in the development of psoriasis, providing a foundation for the discovery of therapeutic strategies and biomarkers.

5. Conclusions

Our study conducted a comprehensive bioinformatics analysis of psoriasis-related genes by integrating three microarray datasets and employing machine learning filtering algorithms. Ultimately, we identified seven candidate genes, including HERC6, SAMD9, SPRR2B, S100A7A, SERPINB4, PI3, and SERPINB3. Further analysis of these candidate genes included transcription factor regulatory network analysis and comprehensive analysis combined with immune cell infiltration characteristics. This research provides strong evidence for the pathogenic mechanisms of psoriasis and lays the foundation for the development of novel biomarkers.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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References

- [1] Barker, J.N. Pathogenesis of psoriasis. *The Journal of Dermatology*, 1998, 25(12), 778-781.
- [2] Fry, L.; Baker, B.S. Triggering psoriasis: the role of infections and medications. *Clinics in Dermatology*, 2007, 25(6), 606-615.

- [3] Bowcock, A.M.; Cookson, W.O.C.M. The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Human Molecular Genetics*, 2004, 13(1), R43-55.
- [4] Bowcock, A.M. The genetics of psoriasis and autoimmunity. *Annual Review of Genomics and Human Genetics*, 2005, 6, 93-122.
- [5] Bhalerao, J.; Bowcock, A.M. The genetics of psoriasis: a complex disorder of the skin and immune system. *Human Molecular Genetics*, 1998, 7(10), 1537-1545.
- [6] Griffiths, C.E.M.; Armstrong, A.W.; Gudjonsson, J.E, et al. Psoriasis. *Lancet (London, England)*, 2021, 397(10281), 1301-1315.
- [7] Gao, X.; Chen, Y.; Chen, M, et al. Identification of key candidate genes and biological pathways in bladder cancer. *PeerJ*, 2018, 6, e6036.
- [8] Ritchie, M.E.; Phipson, B.; Wu, D, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Research*, 2015, 43(7), e47.
- [9] Kolde, R.; Laur, S.; Adler, P, et al. Robust rank aggregation for gene list integration and meta-analysis. *Bioinformatics (Oxford, England)*, 2012, 28(4), 573-580.
- [10] Zhou, Y.; Zhou, B.; Pache, L, et al. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nature Communications*, 2019, 10(1), 1523.
- [11] Chen, B.; Khodadoust, M.S.; Liu, C.L, et al. Profiling Tumor Infiltrating Immune Cells with CIBERSORT. *Methods in Molecular Biology (Clifton, N.J.)*, 2018, 1711, 243-259.
- [12] Janky, R.; Verfaillie, A.; Imrichová, H, et al. iRegulon: from a gene list to a gene regulatory network using large motif and track collections. *PLoS computational biology*, 2014, 10(7), e1003731.
- [13] Mao, X.; Sethi, G.; Zhang, Z, et al. The Emerging Roles of the HERC Ubiquitin Ligases in Cancer. *Current Pharmaceutical Design*, 2018, 24(15), 1676-1681.
- [14] Susana, S.T.; Monica, Cubillos, R.; Taiane, S.; Jose, L.R. Functional and pathological relevance of HERC family proteins: a decade later. *Cellular and Molecular Life Sciences*, 2016, 73, 1955-1968.
- [15] Eszter, S.; Peter, O.; Kornélia, S.; Franco, P.; Zsuzsanna, B.C.; Lajos, K.; Márta, S. Analysis of psoriasis-relevant gene expression and exon usage alterations after silencing of SR-rich splicing regulators. *Exp Dermatol*, 2018, 27(6), 656-662.
- [16] Yao, Y.; Richman, L.; Morehouse, C, et al. Type I Interferon: Potential Therapeutic Target for Psoriasis? *PLOS ONE*, 2008, 3(7), e2737.
- [17] Wang, D.; Duncan, B.; Li, X, et al. The role of NLRP3 inflammasome in infection-related, immune-mediated and autoimmune skin diseases. *Journal of Dermatological Science*, 2020, 98(3), 146-151.
- [18] Hernandez-Beeftink, T.; Guillen-Guio, B.; Lorenzo-Salazar, J.M, et al. A genome-wide association study of survival in patients with sepsis. *Critical Care (London, England)*, 2022, 26(1), 341.

- [19] Nounamo, B.; Li, Y.; O'Byrne, P. et al. An interaction domain in human SAMD9 is essential for myxoma virus host-range determinant M062 antagonism of host anti-viral function. *Virology*, 2017, 503, 94-102.
- [20] Mekhedov, S.L.; Makarova, K.S.; Koonin, E.V. The complex domain architecture of SAMD9 family proteins, predicted STAND-like NTPases, suggests new links to inflammation and apoptosis. *Biology Direct*, 2017, 12(1), 13.
- [21] Johansen, C.; Rittig, A.H.; Mose, M, et al. STAT2 is involved in the pathogenesis of psoriasis by promoting CXCL11 and CCL5 production by keratinocytes. *PLoS ONE*, 2017, 12(5), e0176994.
- [22] Leigh, I.M.; Pulford, K.A.; Ramaekers, F.C, et al. Psoriasis: maintenance of an intact monolayer basal cell differentiation compartment in spite of hyperproliferation. *The British Journal of Dermatology*, 1985, 113(1), 53-64.
- [23] Schön, M.P.; Boehncke, W.H. Psoriasis. *The New England Journal of Medicine*, 2005, 352(18), 1899-1912.
- [24] Chen, H.; Toh, T.K.L.; Szeverenyi, I, et al. Association of skin barrier genes within the PSORS4 locus is enriched in Singaporean Chinese with early-onset psoriasis. *The Journal of Investigative Dermatology*, 2009, 129(3), 606-614.
- [25] Hu, P.; Wang, M.; Gao, H. et al. The Role of Helper T Cells in Psoriasis. *Frontiers in Immunology*, 2021, 12, 788940.
- [26] Ren, Y.; Dong, H.; Jin, R, et al. TRIM22 activates PI3K/Akt/mTOR pathway to promote psoriasis through enhancing cell proliferation and inflammation and inhibiting autophagy. *Cutaneous and Ocular Toxicology*, 2022, 41(4), 304-309.
- [27] Kantaputra, P.; Daroontum, T.; Chuamanochan, M. et al. SERPINB3, Adult-Onset Immunodeficiency, and Generalized Pustular Psoriasis. *Genes*, 2023, 14(2), 266.
- [28] Batycka-Baran, A.; Hattinger, E.; Zwicker, S, et al. Leukocyte-derived koebnerisin (S100A15) and psoriasin (S100A7) are systemic mediators of inflammation in psoriasis. *Journal of Dermatological Science*, 2015, 79(3), 214-221.
- [29] Pauls, K.; Schön, M.; Kubitza, R.C, et al. Role of integrin alphaE(CD103)beta7 for tissue-specific epidermal localization of CD8⁺ T lymphocytes. *The Journal of Investigative Dermatology*, 2001, 117(3), 569-575.
- [30] Kamata, M.; Tada, Y. Dendritic Cells and Macrophages in the Pathogenesis of Psoriasis. *Frontiers in Immunology*, 2022, 13, 941071.



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