Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Core Differentially Expressed Genes in Psoriasis Lesions: An Integrated Analysis of Four GEO Datasets

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Purpose: Psoriasis is a chronic inflammatory skin disease characterized by abnormal keratinocyte proliferation and differentiation, affecting approximately 2% of the global population.

Patients and Methods: This study explored the role of specific molecular biomarkers in the pathogenesis of psoriasis through integrative bioinformatics analysis, aiming to improve diagnostic precision and uncover therapeutic targets. Four independent transcriptomic datasets (GSE34248, GSE41662, GSE50790, and GSE6710) were analyzed using bioinformatics tools to identify consistently dysregulated genes in psoriatic lesions. Subsequently, we constructed a protein–protein interaction (PPI) network using the STRING database and analyzed key gene modules and hub genes involved in disease pathways.

Results: This integrative approach led to the identification of 32 genes consistently dysregulated across all four datasets. Pathway enrichment highlighted significant involvement in biological processes such as keratinization ($p = 1.53 \times 10^{-6}$) and cornified envelope formation ($p = 1.93 \times 10^{-5}$), which are central to the epidermal alterations observed in psoriasis. Several gene families implicated in skin homeostasis and inflammatory regulation were found to contribute to psoriasis pathogenesis.

Conclusion: These findings underscore the relevance of these core genes and pathways in the molecular landscape of psoriasis and offer potential targets for future functional validation and therapeutic intervention.

Keywords: bioinformatic, differentially expressed gene, integrative analysis, keratinization, cornified envelope formation

Introduction

Psoriasis is a chronic, immune mediated inflammatory skin disorder that affects approximately 2% of the global population,[1] with marked variability in prevalence across different geographic groups. A study from Denmark[2] and the US[3] reports a prevalence rate of psoriasis of almost 3%. Guinot et al[4] estimated the prevalence in France at 4.7%.[4] By contrast, the condition appears to be less common in North African countries, with rates ranging between 2.3% and 3%,[5,6] including a documented prevalence of 2.3% in Morocco.[6]

Microarray and high throughput sequencing technologies are robust and reliable approaches for the fast and accurate identification of differentially expressed genes (DEGs) in human patients and animal models. Several platforms exist to generate large scale transcriptomic datasets, which are publicly available in data repositories such as the Gene Expression Omnibus (GEO). These publicly available data sets provide resources for secondary data analysis and hypothesis generation.[7]

In recent years, numerous transcriptomic studies have investigated the gene expression landscape of psoriasis using microarray technologies.[8] These efforts have contributed to a deeper understanding of the molecular mechanisms underlying the disease by highlighting distinct gene expression signatures associated with psoriatic lesions.[8,9]

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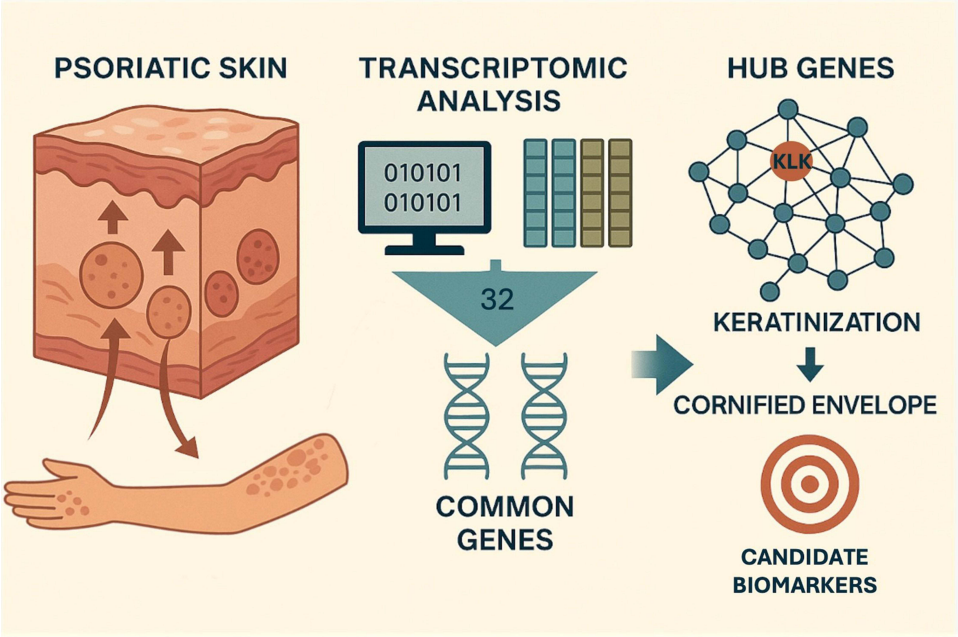
Graphical Abstract



Psoriasis pathogenesis is increasingly recognized as the result of a dynamic interplay between keratinocytes, dermal fibroblasts, melanocytes, and immune cells. Previous large scale analyses of Affymetrix transcriptomic data[10] highlighted not only keratinocyte proliferation but also immune mediated pathways, including IL-17/IL-23, TNF, and JAK-STAT signaling. However, Affymetrix platforms have limitations, as probe coverage is incomplete and novel genes or isoforms cannot be identified.[10]

More recent reviews have emphasized the central role of inflammatory triggers and cytokine signaling networks.[11,12] Topical corticosteroids, a cornerstone of treatment of psoriasis, exert broad anti-inflammatory effects primarily by binding to cytosolic glucocorticoid receptors, leading to the transrepression of key pro-inflammatory transcription factors like NF-κB and AP-1, thereby suppressing the production of cytokines (eg, IL-17, IL-23, TNF-α) and mediating vasoconstriction. Vitamin D analogues such as calcipotriene also widely used in the psoriasis treatment, act by binding to the vitamin D receptor, modulating keratinocyte differentiation and proliferation, and also exhibit immunomodulatory properties by inhibiting T-cell activation and the Th17 pathway.[13] Novel biologic and small molecule therapies represent a paradigm shift towards precision targeting, with agents designed to neutralize specific cytokines central to the IL-23/Th17 axis or inhibit intracellular signaling pathways (PDE4 inhibitors, JAK-STAT inhibitors), thereby disrupting the inflammatory cascade at a more upstream and specific point compared to conventional treatments.[14]

For this purpose, we performed an analysis of four transcriptomic datasets to determine commonalities across different datasets to underscore the relevant pathways in the molecular landscape of psoriasis and offer potential targets for future functional validation and therapeutic interventions.

Methods

Psoriasis Gene Expression Data Sources

A comprehensive search for psoriasis vulgaris gene expression data was conducted on the NCBI GEO database, focusing exclusively on publicly available human skin biopsy samples. This study was exempted from ethical approval by Sfax University in Tunisia, as it was based exclusively on the analysis of publicly available data and did not involve direct

contact with human participants or access to identifiable personal information. The search utilised keywords such as "Psoriasis vulgaris" and "RNA", yielding 125 datasets, of which only 14 met the inclusion criteria: mRNA expression data from naïve patients, obtained from lesional skin biopsies, and compared with healthy control skin. Datasets were excluded if they involved miRNA, non-coding RNA, pre-treated patients, RNA sequencing from cultured keratinocytes, or perilesional skin samples. Ultimately, seven datasets were initially selected, and four were retained for final analysis as they specifically compared lesional vs. non-lesional skin. These included GSE34248 and GSE41662,[15] GSE50790,[16] and GSE6710.[17] The excluded datasets were omitted due to their inclusion of control samples.

Identification of Differentially Expressed Genes

An online interactive web tool, GEO2R,[18] was used to analyze the raw data of microarrays and identify DEGs between patient groups. GEO2R uses moderated t-statistics to compare gene expression levels in different groups. The p-value < 0.05 and logarithmic fold change $|\log2FC| \geq 2$ were used as the threshold to obtain statistically significant DEGs. Hence, upregulated genes (p-value < 0.05, $\log2FC \geq 2$) and downregulated genes (p-value < 0.05, $\log2FC \leq -2$) were grouped depending on their expression levels in respect to the cut-off values. Importantly, prior to cross-dataset comparison, each platform's probe identifiers were first mapped to their corresponding official HGNC Gene Symbols using the platform-specific annotation tables available within GEO2R. All subsequent integration and Venn diagram intersections were therefore performed at the Gene Symbol level, not at the raw probe level, ensuring valid cross-platform comparability.

The identification of Differentially Expressed Genes (DEGs) was initiated by analyzing the raw microarray data, with gene expression levels compared between samples. This was achieved using the publicly available online interactive web tool, GEO2R,[18] which simplifies the differential expression analysis for publicly archived GEO datasets. GEO2R was configured to utilize the GEOquery package for parsing the processed data into R structures, and subsequently, the robust limma (Linear Models for Microarray Analysis) package was employed. The analysis relied on moderated t-statistics from limma for testing, which intrinsically handles multiple-testing corrections on p-values to mitigate the occurrence of false positives.

To define the DEGs, stringent cut-off values were applied. The filtering process included the following steps: Statistical Significance Filter: A p-value <0.05 was required. This criterion was used to establish that the change in expression was unlikely to have occurred by chance. Magnitude of Change Filter: A minimum absolute logarithmic fold change of $|\log2FC| \geq 2$ was set, defining a substantial difference in expression. Gene Classification: Genes were subsequently classified as either upregulated (p-value <0.05 and $\log2FC \geq 2$) or downregulated (p-value <0.05 and $\log2FC \leq -2$). These stringent thresholds were applied deliberately to ensure that only the most prominent probes were identified, confirming that the final list of DEGs reflected the most substantial alterations in the transcriptome.

Experimental Design

The grouping within the datasets was kept unmodified as described in each corresponding dataset. This allowed for the pooling of the probesets from the three datasets in respect to their pathology in two subgroups. The first subgroup corresponded to patients with lesions (lesional - L).

The second group was composed of the same patients' skin biopsies without lesions and was grouped as non-lesional (NL). Patient numbers in each dataset, general information on GEO datasets, and platforms are provided in Table S1. Lesional and non-lesional samples of each dataset are listed in Table S2.

Analysis of Differential Gene Expression Subgroups

Following the initial data processing, the pooled sample collection was organized into the three defined pathology groups: control (Ctl), lesional (L), and non-lesional (NL). A key focus of the study was the comparison between the two patient derived subgroups, L and NL. Specifically, differential gene expression analysis was conducted by comparing the L group against the NL group. This intra-patient comparison was performed to isolate the gene expression changes specifically associated with the active psoriatic lesion, thereby minimizing variation introduced by differences in genetic background or systemic factors between individuals. Up and downregulated probes were visualized with volcano plots using the bioinfokit tool.[19] Common DEGs for up and downregulated probesets in the four datasets were identified with online tool

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"Bioinformatics and Evolutionary Genomics" and visualized using Venn diagrams.[20] The intersection was performed exclusively at the annotated Gene Symbol level, using the platform specific annotation tables provided within GEO2R. This conservative vote counting strategy maximizes specificity, yielding a high confidence core signature of consistently dysregulated genes across all four independent datasets.

Protein–Protein Interaction Network Construction, Functional Enrichment, and Pathway Analysis

Protein–protein interaction (PPI) networks were constructed for differentially expressed genes (DEGs), followed by Gene Ontology (GO) enrichment and pathway analysis of up- and downregulated probe sets using the Enrichr classification system.[21] Enrichr, a user-friendly gene set enrichment analysis tool, facilitated the functional annotation of DEGs across three GO categories: biological processes (BP), molecular functions (MF), and cellular components (CC). Additionally, Enrichr enabled comparative pathway analysis by integrating multiple pathway resources, ensuring a comprehensive interpretation of functional associations. To further investigate protein interactions, a PPI network was generated using the STRING database (https://www.string-db.org/), with the organism parameter set to *Homo sapiens*, allowing the retrieval and analysis of the minimum required interaction score at high-confidence (0.700) PPI data. Additionally pathways including *KLK13* probe, formation of the cornified envelope, keratinization, and developmental biology, were clustered using k-means analysis.

Results

Differential Expression Analysis

The up- and downregulated probe sets for each dataset were visualized using volcano plots (Figure S1). Among the statistically significant differentially expressed probe sets across the four datasets (GSE34248, GSE41662, GSE50790, and GSE6710), a comparative analysis using Venn diagrams identified 32 and 3 major overlapping up and down regulated probe sets respectively (all identified using nominal p-value < 0.05 and $|\log2FC| \geq 2$ per dataset, the requirement for concordance across four independent datasets served as the primary stringency filter) in the L vs. NL comparison across studied datasets (Figure 1). In Tables 1 and 2 are mentioned the identified upregulated and down-regulated genes respectively. Interestingly, among them, several genes are involved in keratinization and cornified envelope formation. Among the 32 upregulated genes, notable examples include TGM1 (present in all 4 datasets), KRT16 (4/4 datasets), DSC2 (4/4 datasets), and S100A7 (4/4 datasets), all well-established markers of keratinocyte activation and epidermal remodeling. KLK13, also consistently upregulated across all four datasets, was identified as one

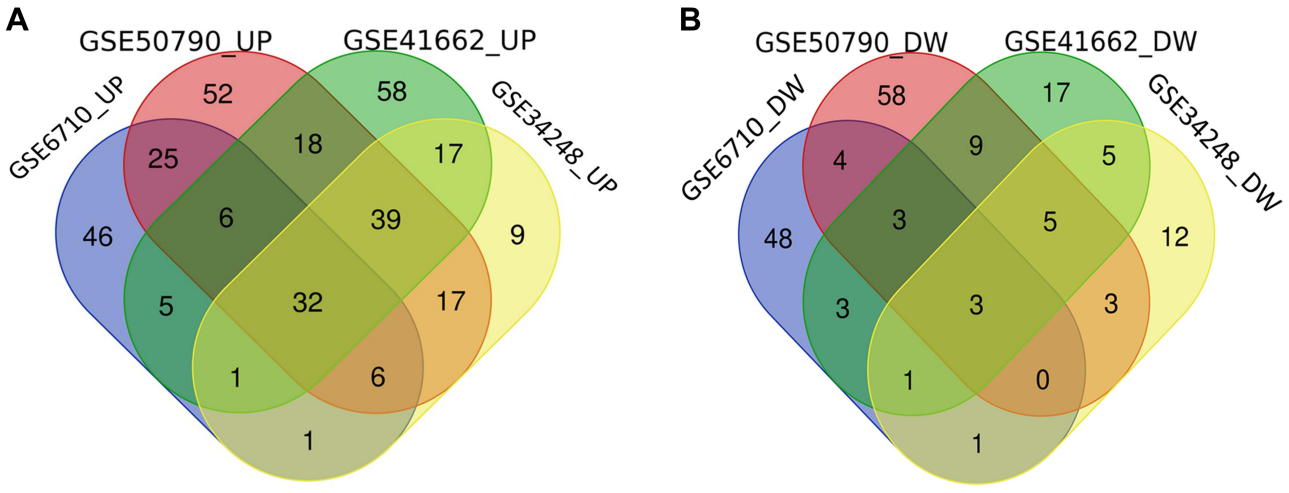

Figure 1 Venn's diagram showing the common (**A**) upregulated, and (**B**) downregulated DEGs from across four datasets. The number of probes at each junction of four datasets is indicated within the intersections. Pathway analyses were undertaken for all commonalities; however, the intersection across four datasets for upregulated and downregulated DEGs was evaluated in greater detail (L, lesional; NL, non-lesional).

Table 1 The Total Number and List of Common Probesets of Up-Regulated Probesets in Respect to Venn Analysis

	Intersection of Datasets	Total Number of Common Genes	Gene List
Upregulated Probes	GSE34248_UP GSE41662_UP GSE50790_UP GSE6710_UP	32	TGM1 MPZL2 EHF ARSF KLK6 SPRR2C CD24 CXCL13 SERPINB13 AKR1B10 KYNU TCN1 UPP1 ADAMDEC1 KLK13 FOXE1 HPSE CHI3L2 SAMD9 LCN2 OAS2 IL36G KRT16 RRM2 SERPINB3 HYAL4 PI3 DSC2 STAT1 CXCL8 RGS1
	GSE41662_UP GSE50790_UP GSE6710_UP	6	CARHSP1 HS3ST3A1 MXD1 CXCL2 CCL4 LTF
	GSE34248_UP GSE50790_UP GSE6710_UP	6	GK ATP12A GM2A HERC6 SERPINB4 RHCG
	GSE34248_UP GSE41662_UP GSE6710_UP	1	OAS1
	GSE34248_UP GSE41662_UP GSE50790_UP	39	DEFB4A RSAD2 DEFB103A ADH7 GDA UGT1A1 NAMPT UGT1A9 SPRR3 UGT1A8 INA REN KLK8 PGBD5 DEFB103B VNN1 S100A7A FUT3 CLEC7A EPSTI1 PRSS27 TMC5 LINC01215 KCNJ15 GBP6 KLHDC7B GZMB KLK9 CD274 DEFB4B OASL CYP24A1 UGT1A3 UGT1A5 SPRR2B C10orf99 IGFL1 FAM83A ARNTL2
	GSE50790_UP GSE6710_UP	25	IL17A PPARD TNIP3 STEAP4 TREX2 ZC3H12A MX1 WWTR1 SOD2 MIR6732 CCL18 LOC100129518 TMPRSS4 CCL20 HAUS7 IFI44L S100A12 TMPRSS11D CXCL1 FOSL1 MMP1 TYMP CHAC1 ISG15 VNN3
	GSE41662_UP GSE6710_UP	5	MKI67 KLK10 KIF20A SPTLC2 TRIM15
	GSE34248_UP GSE6710_UP	1	TGFA
	GSE41662_UP GSE50790_UP	18	HAS3 KRT24 LOC101928317 NETO2 CCL3L3 APOBEC3A GALNT6 PLBD1-AS1 CCL3L1 APOBEC3A_B SLC7A11 CCL3 EPHB2 SERPINA1 SLC26A9 MMP12 BCL2A1 PLA2G4E-AS1
	GSE34248_UP GSE50790_UP	17	IL19 PLA2G2F LRRC55 CXCL6 AIM2 CHRNA9 CTLA4 LIPG ADAM23 LOC100507140 HTR3A HAL TEX101 CCR7 NWD2 S100A9 TRIM10
	GSE34248_UP GSE41662_UP	17	PRKCQ LRG1 LOC100289094 ARG1 RNASE7 UGT1A7 UGT1A10 UGT1A4 RDH16 UGT1A6 PPIF CXCL9 S100A8 FUT6 RALGPS2 PRR9 PRKCQ-AS1
	GSE6710_UP	46	CDH3 IFI16 LOC101928269 STS PITX1 RAB27B EHBP1L1 PML ARHGDIA IRF7 STAT3 XAF1 SMC3 AASS SQLE CTRB2 BCLAF1 CYP2E1 GK3P SYK ELL2 LOC100506403 SBNO2 TWF1 CDC20 RAB35 APOL1 NDC80 TOP2A C1orf116 ZFY CTRB1 SLC6A14 MCL1 ALDH3B2 RUNX1 PTPN2 TTC22 NABP1 PRDM1 LTB4R LYPD1 IL1RN MTF1 RBBP6 ZFX
	GSE50790_UP	52	IL26 OAS3 GPR158 S100P PLA2G4D SLC16A9 BATF2 IL20 PCSK1 PI15 POLR3G THY1 CD177 ADCYAP1 IFI6 LINC00518 FCGR1A CYP7B1 WNT5A CYP27B1 FCGR1CP APOL6 SELL ICOS LINC01206 IL1B IL12B SOST ADGRF1 MIR31HG STEAP1B IFNG LUZP2 CLDN17 IL24 IL36A FUT2 CYP4Z2P STMN2 RND1 KRT37 LOC101928231 LHFPL3-AS1 IL1RL1 FCGR1B RTP4 FCHSD1 MIR3945HG CXCL17 DSG3 FPR1 IFI27
	GSE41662_UP	58	TMEM171 XDH CDSN PDZK1IP1 IL36RN KCNK10 CLSPN DEPDC1B TMEM45B C15orf48 CCNB1 PKP1 TAB3 RGS20 SLC23A2 C12orf56 PRSS2 TMEM86A SLC5A1 RAB27A WFDC12 FBXO45 EPHX3 BIRC5 MCM10 SLURP1 TGM3 CDH26 A2ML1 LCE3D TTC39A CYP2C18 EREG CNFN C9orf84 LRP8 PRSS3 ACPP DDIAS CXCR2 PCP4L1 HMMR-AS1 SPRR1A MUC4 TXNRD1 IVL ABCA12 SERPINB7 FLVCR2 LYPD5 LINC01214 SLC16A10 SPRR1B SH3PXD2A-AS1 ALOX12B DLGAP5 CYSRT1 CRCT1
	GSE34248_UP	9	CXCL10 HSD17B2 LOC100505570 SLC6A11 CYTH3 TNFAIP2 LYZ NLRP7 SKA1

component of the broader protease network. Among the 3 downregulated genes, MMP20 and KLK4 were identified in the 3-dataset overlap (GSE34248, GSE41662, GSE6710).

Pathway Analysis

Pathway enrichment analysis using EnrichR tools to identify key biological pathways associated with commonly upregulated and downregulated probesets in the L vs. NL skin comparison. Among the most significantly upregulated genes (n = 32), the "Formation of Cornified Envelope" pathway ranked as the top pathway, followed by "Keratinization". Additionally, "Neutrophil Degranulation" was the immune related pathway linked to psoriasis, appearing in the seventh position (Figure 2a). These findings confirm that keratinization and cornified envelope formation represent the primary and most statistically robust biological processes dysregulated in psoriatic lesions ($p = 1.53 \times 10^{-6}$ and $p = 1.93 \times 10^{-5}$, respectively). The "Neutrophil Degranulation" pathway, in which KLK13 participates, represents a secondary immune-related finding. Conversely, among the commonly downregulated probe sets, pathways related to "Mitochondrial Uncoupling" were among the top 10 statistically significant pathways (Figure 2b). The combined power of datasets and patients revealed evident downregulation of glucocorticoid pathways "prednisone ADME" and "glucocorticoid biosynthesis", which are currently a targeted therapy for psoriasis.[22]

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Table 2 The Total Number and List of Common Probesets of Down-Regulated Probesets in Respect to Venn Analysis

	Intersection of Datasets	Total Number of Common Genes	Gene List
Downregulated probes	GSE34248_DW GSE41662_DW GSE50790_DW GSE6710_DW	3	WIF1 BTC
	GSE41662_DW GSE50790_DW GSE6710_DW	3	TNMD MSMB HSD11B1
	GSE34248_DW GSE41662_DW GSE6710_DW	1	RBP4
	GSE34248_DW GSE41662_DW GSE50790_DW	5	ZDHHC11B ZDHHC11 WDR72 THRSP PM20D1
	GSE50790_DW GSE6710_DW	4	CDHR1 GSTA3 IL37 CCL27
	GSE41662_DW GSE6710_DW	3	GPD1 LEP SCGB2A1
	GSE34248_DW GSE6710_DW	1	MUC7
	GSE41662_DW GSE50790_DW	9	DIRAS2 LMO3 TMEM56 ACADL TNNI2 RORC SP8 TPPP RAB3B
	GSE34248_DW GSE50790_DW	3	SPINK1 MYOC ANKFN1
	GSE34248_DW GSE41662_DW	5	PAMR1 SLC14A1 PHYHD1 FOLR1 OPRPN
	GSE6710_DW	48	ITM2C ITGA7 PTPN21 TPPP3 FAM149A CYP27A1 KCNAB1 TSPAN8 IFT122 TIMP4 MMP28 TOX3 GLRB TIMM17A ADGRL3 FABP7 EZH1 PARD3 ATRIP CHP2 LMOD1 TREX1 FADS1 DES SMIM7 PIP SCGB1D2 SYNE1 CRY2 ABCF2 SLC47A1 PPP1R1A FAM107A MIR1908 SERHL2 APOC1 ENO2 FADS2 NRTN HCFC1R1 RERGL P2RX1 ATP2A3 GPRC5A BST1 LOC101927266 AGR2 SUPT20H
	GSE50790_DW	58	CA3 NPY5R SAPCD1 LEPR LOC101928349 FAM153A ABCB5 TMEM255A BTBD16 SCIN ATP13A5 LEPROT FAM153C SLC1A6 PACRG CCKBR ANKRD18A CSMD1 CRAT MORF4L2-AS1 LOC101930363 SGSM1 GRIN2A EGF MYH14 MACROD2 AQP9 PHYHIP AGR3 KRT77 FAM201A ADAMTSL3 ACTC1 LOC100507387 FAM153B C5orf46 SYT8 SLCO4C1 MSH5-SAPCD1 SYT17 CAPZA3 GLDC HS3ST6 JRK C1QTNF7 KLK1 CYP4B1 PAK3 SLC27A2 HHATL GREB1L ABCA13 FAR2 ACSBG1 GALNT15 SYN2 FGF9 LOC101927870
	GSE41662_DW	17	ERBB4 TTYH1 WNK2 HMGCS2 RIMS1 MAP6 LOC284825 MYO3A ANKRD33B POSTN CHAD PCK1 WFDC2 HIF3A PDE11A PLIN1 ADIPOQ
	GSE34248_DW	12	FUT9 SLC6A2 DENND2A GRIA4 ZSCAN18 LIPE UPK1B TNN COCH MARC1 GLYAT NELL1

Hub Protein Identification

For the L vs. NL skin comparison, hub genes were identified using the STRING database, and the PPI network was visualized (Figure 3). K-means analysis of upregulated genes revealed three interrelated clusters, primarily encompassing genes involved in skin formation, maintenance, and immune system activation (Figure 3a). In contrast, analysis of downregulated genes identified eight clusters, with six exhibiting interrelated functional associations (Figure 3b).

Discussion

To date, several genes have been implicated in psoriasis vulgaris described as a common autoinflammatory genetic disease. The known involved genes play critical roles in inflammatory responses, keratinocyte differentiation and skin barrier function.[23–27]

Our analysis identified 32 consistently upregulated genes across four datasets, many of which are involved in keratinization and cornified envelope formation, confirming earlier findings.[10] Tables 3 and 4 present all significantly upregulated and downregulated genes, along with annotation in red indicating genes that were previously reported versus newly identified probes.

This study revealed multiple genes potentially involved in the pathophysiology of the disease. The common 32 genes among 4 datasets revealed numerous pathways, among which the first and second most statistically significant were keratinization (p-value = 1.53E-6) and cornified envelope formation (p-value = 1.93E-5). Statistically significant

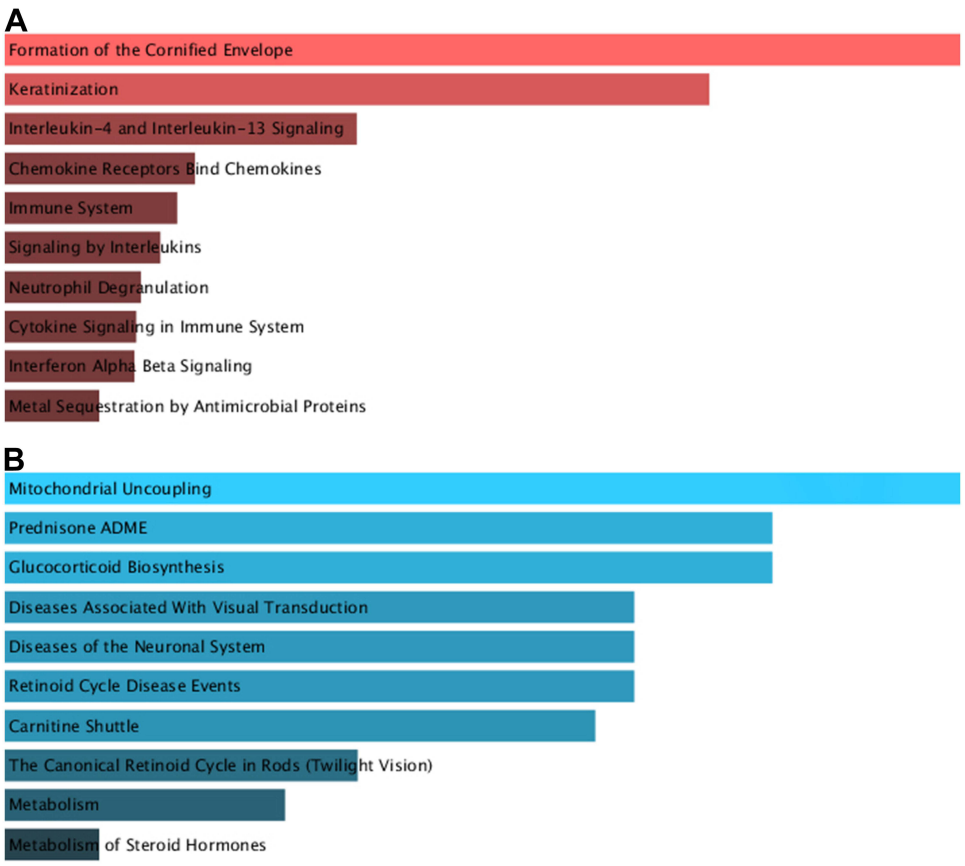

Figure 2 Enrichr Pathway Enrichment Analysis: Highest-Ranked Significant Pathways for (**A**) Up and (**B**) Down Regulated Genes.

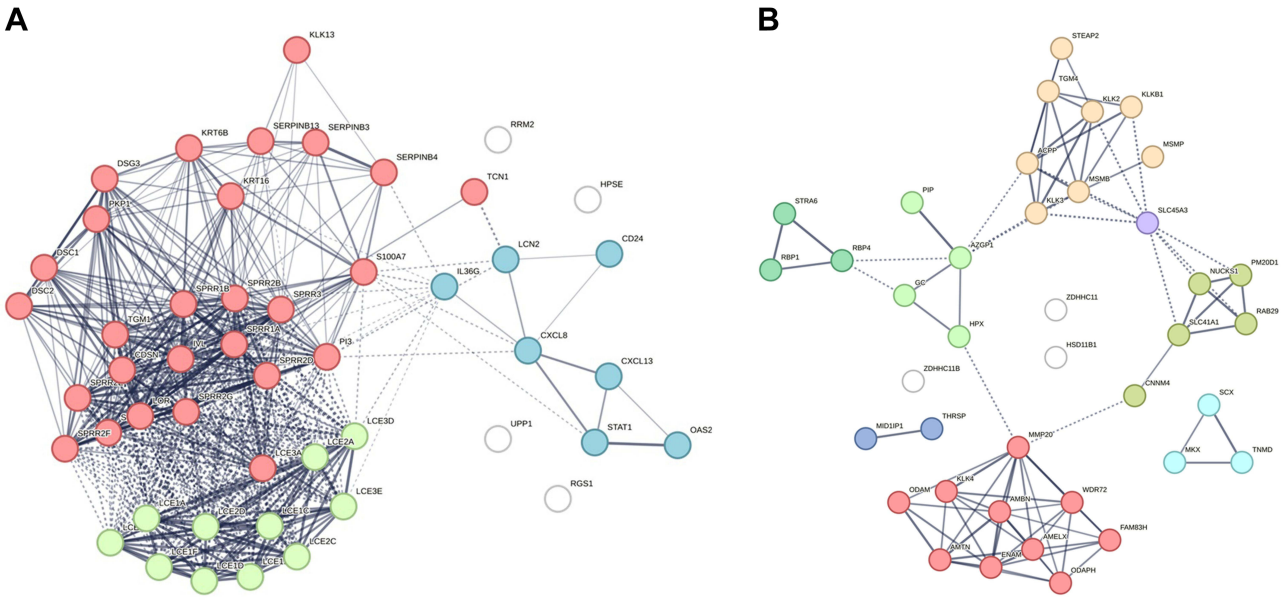

Figure 3 PPI network and K-means clustering were conducted using pathways that included KLK13 (**A**) upregulated genes identified three major interrelated clusters, (**B**) downregulated genes identified six clusters. Each circle represents a probe.

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Table 3 The Most Differentially Up-Regulated Genes in Lesional Psoriatic Skin Compared to Healthy Skin. Red-shaded Boxes Indicate Genes Commonly Identified Across Datasets

Bowcock et al[28]	Kulski et al[29]	Mee et al[30]	Gudjonsson et al[31]	Gudjonsson et al[32]	Li et al[9]	Ahn et al[33]	Pasquali et al[34]	This Study
S100A2	JUNB	SERPINB4	C10orf99	SERPINB4	DEFB4A	IL36A	PI3	TGM1
S100A7	LAMP3	PI3	SPRR2B	DEFB4	S100A7A	SPRR2F	DEFB4A	MPZL2
S100A8	*YWHAB*	S100A9	S100A7	S100A7L1	PI3	SPRR2A	SERPINB4	EHF
S100A9	SEC61G	S100A7	LCE3D	PI3	LCE3A	SERPINB4	TCN1	ARSF
SPRR2A	KIAA0101	DEFB4	SPRR2G	SERPINB3	S100A12	S100A7A	DEFB4B	KLK6
SPRR1B	CSTA	KRT6A	WFDC12	SPRR2C	S100A9	SPRR2B	S100A9	SPRR2C
SPRK	OAS1	SERPINB3	S100A9	AKR1B10	SERPINB4	PI3	AKR1B10,	CD24
CSTA	CCL20	SPRR2B	HAL		TCN1	TCN1	S100A7A	CXCL13
FABP5	TGM1	KRT17	IL1F9	S100A12	S100A8	S100A9	KYNU	SERPINB13
DEFB2	SEC61B	KRT16	DEFB4	S100A9	CXCL8	KRT6C	SERPINB3	AKR1B10
KRT6A	GBA	SPRR2A		C10orf99	TMPRSS11D	TMPRSS11D	IFI6	KYNU
IFI27	H2AFY	SPRR2D		KYNU	S100A7	HEPHL1	SPRR2A	TCN1
KRT16A	UBE2L6	GJB2		LCE3D	SPRR2F	SPRR2D	IFI27	UPP1
KRT17	GM2A	KRT6E		S100A7	TNIP3	IL17F	OAS2	ADAMDEC1
SERPINB3	SULT2B1	KRT6B		CXCL8	SERPINB3	C10orf99	IFI44L	KLK13
SERPINB4	P4HB	CSTA		KRT16	HEPHL1	LCE3E	C10orf99	FOXE1
	RER1	SPRR1B			GDA	KRTAP9-7	IFI44	HPSE
	PSMB6	TCN1			AKR1B10	LCE3D	HEPHL1	CHI3L2
	NMI	SPRR1A			CXCL13	AKR1B10	EPGN	SAMD9
	IVL	CD24			SPRR2A	KRTAP13-1		LCN2
		LCN2						OAS2
		SPRR2E						IL36G
		FABP5						KRT16
								RRM2
								SERPINB3
								HYAL4
								PI3
								DSC2
								STAT1
								CXCL8
								RGS1

pathways showed increased upregulation for *TGM, KRT16*, and *DSC2*, which were further analyzed to understand their importance in psoriatic lesional skin biopsies.

TGM1, encoding transglutaminase 1, is essential for forming the cornified envelope during terminal keratinocyte differentiation, and its dysfunction compromises skin barrier integrity, contributing to disease onset.[35] KRT16, a type I

Table 4 Significantly Down Regulated Genes in Lesional Psoriatic Skin Compared to Healthy Skin. Red-shaded Boxes Indicate Genes Commonly Identified Across Datasets

Bowcock et al[28]	Kulski et al[29]	Mee et al[30]	Gudjonsson et al[31]	Gudjonsson et al[32]	Li et al[9]	Ahn et al[33]	Pasquali et al[34]	This Study
KRT15	CSPG4	HBB	ELOVL3	WIF1	AADACL3	*ADAMTS16*	FAM26E	WIF1
JUND	ANP32A	HBA2	FLJ32569	BTC	PM20D1	*CYP2W1*	NR4A3	BTC
XP5	SPTAN1	KRT2A	HSD3B1	THRSP	DGAT2L6	*FOS*	KRT77	
TNA	C11orf11	ZNF91	MLSTD1	IL1F7	AWAT2	*CSF3*	HIST2H4B	
CRIP1	SSA2	MUC5B	GAL	CCL27	AWAT1	*BTC*	APOD	
COL1A2	LAMA5	MT1X	KRT6L	KRT1B	PNPLA5	C16orf89	CA6	
GSN	ICA1	GATA3	THRSP	MSMB	ROS1	FAM95C	KRT31	
PCBP2	MECP2	LOR	FADS1	ELOVL3	GAL	MATN4	ATF	
LGALS3	ALDH3A2	ACTA2	MUC7	GAL	CYP2W1	PDK4,	ZNF667-AS1	
HBA1	NAB1	SFTPA2	SCGB2A1	FABP7	UGT3A2	KRT77	TNFAIP3	
MT1L	DDHD2	CST6		ACSBG1	C10orf129	CILP2	C5orf46	
DF	ANXA8	TXNIP		MLSTD1	PDE6A	UGT3A2	FTL	
LGALS1	ZNF384	MBP		HS3ST6	BTC	BMP3	CLDN8	
	OSBPL1A	LGALS3		WDR72	TRIM55	NR4A1	CRABP1	
	ZBTB16	MUC6		SERPINA12	WIF1	WNT2	AGR2	
	ATXN3				ELOVL3	MAB21L1	CDA	
	DDR1				HGD	HAS1	PPAP2A	
	GPM6B				HAO2	SERPINE1	TRAM2	
	KCNC1				SYT9		CRYAB	
	PCDH21				LPPR5		AF212831.2	
					SERTM1			
					IL6			

keratin, is markedly overexpressed in psoriatic lesions, where it promotes keratinocyte hyperproliferation and abnormal differentiation,[36] inflammation, though its dysregulation can enhance immune responses and tissue damage.[37]

Importantly, when comparing our results to previous studies, we also detected immune-related mediators such as CXCL8, CCL20, and IL36G, which have established roles in neutrophil recruitment, IL-17–driven inflammation, and epidermal crosstalk.[11] Enrichment analysis further revealed activation of IL-17, IL-23, NF-κB, and JAK-STAT pathways, consistent with current therapeutic targets in psoriasis.[12] These results highlight that psoriasis is not limited to keratinocyte hyperproliferation, but rather reflects coordinated deregulation of keratinocyte, immune cell signaling. *KLK13* was also upregulated and identified in "Developmental Biology" (p-value = 0.017). Dysregulation of the KLK cascade is responsible for skin inflammatory diseases (Figure 4). KLK are serine proteases encoded by 15 different genes. Abnormal activation of the KLK proteolytic cascade is reported in psoriasis. In atopic dermatitis, an inflammatory skin disease, the upregulation of some KLK may induce activation of NK-κβ pathway and IL-8.[38]

The serine protease inhibitor PI3 (elafin) is also upregulated in psoriasis, acting to regulate protease activity and mitigate inhibitors to protect tissues from damage caused by excessive leukocyte activity.[39] Through this mechanism, elafin may influence the activity of kallikrein related peptidases such as KLK13, which is also upregulated in psoriasis. KLK13 may modulate epidermal desmosomal adhesion by proteolytically processing DSC2,[40] a desmosomal cadherin critical for keratinocyte cohesion.[41] Disruption in these pathways through genetic mutation or altered expression

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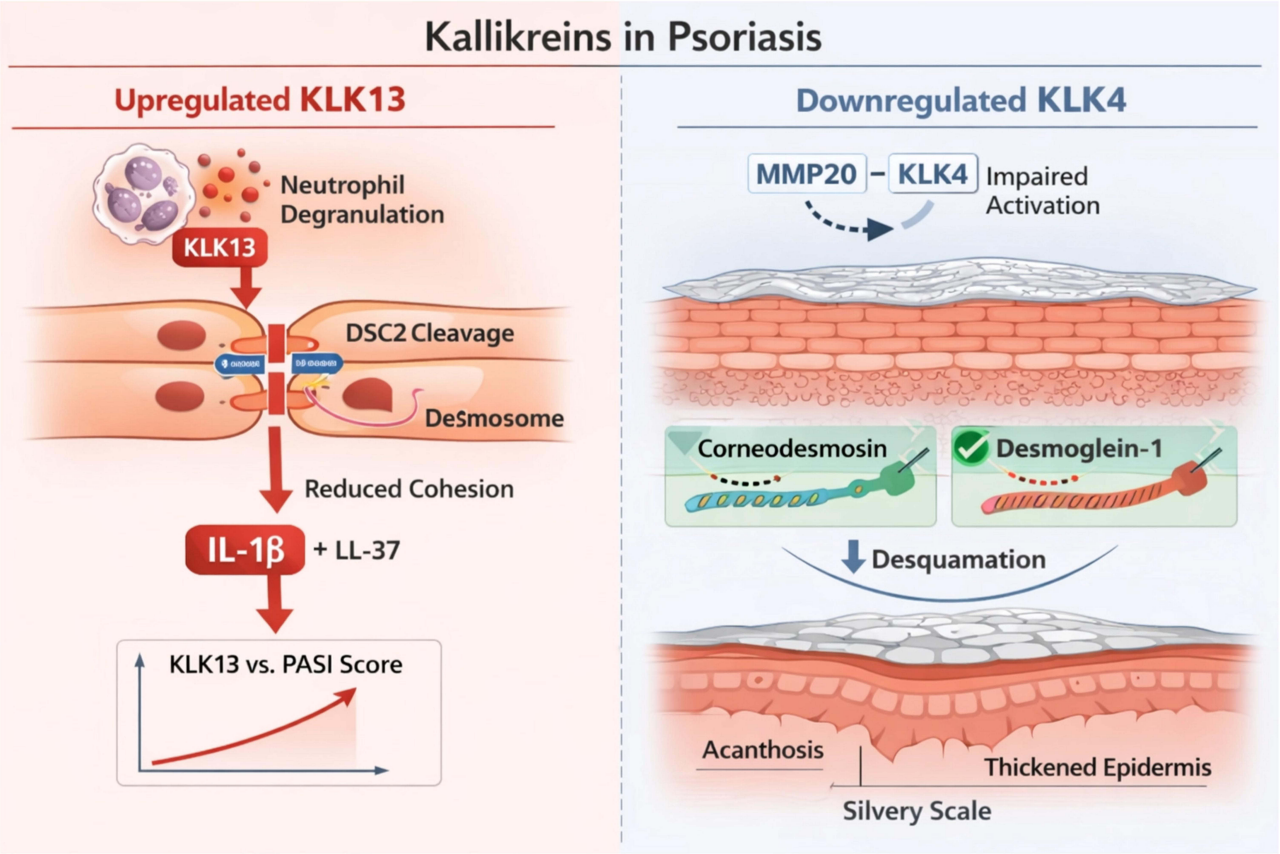

Figure 4 Dysregulated Kallikrein (KLK) Signaling in Psoriasis Pathogenesis. Left (KLK13 Upregulation): Increased KLK13 promotes neutrophil degranulation and IL-1β activation (amplified by LL-37). Proteolytic cleavage of Desmocollin-2 (DSC2) by KLK13 reduces keratinocyte cohesion. Right (KLK4 Downregulation): Impaired MMP20-KLK4 axis activation leads to reduced cleavage of Corneodesmosin and Desmoglein-1, inhibiting physiological desquamation.

underlies the chronic inflammation, abnormal keratinocyte behavior, and skin barrier dysfunction that characterize psoriasis. Notably, KLK13 is enriched in the "Neutrophil Degranulation" pathway ($p = 0.006$) and contributes to IL-1β activation via neutrophils,[42] a response that can be amplified by LL-37 in psoriatic skin.[43] Both elafin and KLK13 are upregulated in lesional and non-lesional psoriatic skin,[44,45] with serum KLK13 levels correlating with Psoriasis Area Severity Index scores.[45]

To investigate the molecular interactions among the key genes implicated in psoriasis, a STRING analysis was performed to map their functional network. The results revealed that these genes are interconnected not only with one another but also with genes from the top ten statistically enriched downstream pathways (Table 2 and Table 4), suggesting a broader functional network underlying disease pathology. These pathways were significantly associated with interleukin signaling ($p = 6.85 \times 10^{-4}$), chemokine receptor activity ($p = 0.003$), and immune system regulation ($p = 0.004$), highlighting their roles in mediating inflammatory responses. Notably, CXCL8 (IL-8), STAT1, and LCN2 emerged as central hub genes within these pathways. CXCL8 is a chemokine crucial for neutrophil recruitment and activation, processes that are heightened in psoriatic skin due to increased CXCL8 expression by keratinocytes, thereby amplifying local inflammation.[46] STAT1, a pivotal transcription factor in the JAK-STAT signaling cascade, orchestrates responses to interferons and other cytokines, with its upregulation and post-translational modification previously confirmed in psoriatic lesions.[47,48] LCN2 (lipocalin-2) contributes to innate immunity and modulates both neutrophil function and keratinocyte behavior, reinforcing its relevance in psoriasis pathogenesis.[49]

Similar regulation is observed with other kallikreins, such as KLK4, which can cleave corneodesmosin, desmocollin-1, and desmoglein-1, key proteins involved in desquamation and epidermal integrity. Furthermore, transglutaminases (TGM1, TGM3, and TGM5) in the epidermis are essential for skin barrier formation and are activated by cathepsin D.

Mutations in these enzymes lead to distinct skin disorders, including ichthyosis (TGM1), hair abnormalities (TGM3), and acral peeling skin syndrome (TGM5), emphasizing the broader relevance of protease regulation in skin homeostasis.

While our strict four-dataset intersection yielded a limited number of commonly downregulated genes, analyzing the intersection of three datasets (GSE34248, GSE41662, and GSE6710) revealed additional biologically relevant patterns, notably the coordinated downregulation of the MMP20-KLK4 protease axis. MMP20 is known to activate pro-KLK4, which subsequently activates other kallikrein zymogens crucial for maintaining epidermal homeostasis and desquamation. The concurrent downregulation of MMP20 and KLK4 observed in this three dataset overlap suggests a disrupted proteolytic activation cascade that may impair normal epidermal remodeling. Furthermore, other downregulated genes identified in this subset, such as TGM4, SLC41A1, and SLC45A3, point to altered keratinocyte function and ion transport. However, because these targets did not meet our stringent four dataset core criteria, their role in psoriasis pathogenesis requires cautious interpretation and highlights the need for further functional validation to confirm their biological relevance.

Further analysis of datasets GSE50790 and GSE6710 revealed downregulation of leptin (LEP), a hormone with wide-ranging effects on skin physiology. Leptin receptors have been identified in the epidermis, particularly in basal keratinocyte and in dermal papilla cells of hair follicles.[50] Leptin promotes keratinocyte and fibroblast proliferation, facilitates epithelialization, and enhances collagen synthesis, all of which are essential for skin regeneration and barrier maintenance.[51] Additionally, leptin upregulates human β-defensin 2, reinforcing the skin's antimicrobial defence.[52] However, literature reports on leptin levels in psoriasis are conflicting; patients with severe psoriasis often exhibit elevated leptin levels, whereas those with milder forms may show reduced expression.[52] In our analysis, leptin was consistently downregulated across both datasets, alongside adiponectin (GSE41662), another adipokine with anti-inflammatory properties. This dual downregulation may contribute to impaired immune regulation and barrier dysfunction in psoriatic skin. However, because disease severity was not stratified in the datasets, direct comparisons across samples remain limited. Additionally, among the downregulated pathways was "carnitine shuffle", which is essential for the transport of long chain fatty acids through the membrane of mitochondria, which is crucial for skin beta-oxidation supply, pointing to an increased energy demand, that potentially cannot be maintained due to pathology. Collectively, the observed downregulation of key proteases, differentiation regulators, transporters, and adipokines underscores a systemic shift away from normal epidermal homeostasis and immune competence in psoriasis. These findings highlight potential targets for future functional studies aimed at restoring skin integrity and modulating inflammation.

A significant finding of this study is that if prospective trials incorporate evaluations of patient severity, drug targets may be addressed with enhanced specificity and effectiveness.

A notable methodological limitation of this study is our reliance on the direct intersection of independently generated DEG lists (the Venn diagram approach) rather than employing a formal pooled meta-analysis algorithm (such as RankProd or DERGA). While our stringent intersection criteria successfully isolated a highly robust core signature of 32 upregulated genes, this conservative approach is mathematically susceptible to the limitations and size of the smallest dataset, inevitably yielding a higher false-negative rate. Consequently, our analysis represents a highly filtered subset of biomarkers, and it is highly likely that many biologically relevant genes that a standard meta-analysis would detect were excluded. Future studies integrating raw expression matrices to calculate pooled effect sizes are warranted to capture the broader, more comprehensive transcriptomic landscape of psoriasis.

Conclusion

The use of Affymetrix microarrays may impose important limitations, including incomplete probe annotation and the inability to detect novel transcripts. This may explain why several well-established psoriasis-associated genes (eg, IFNAR1, IFNAR2) were not consistently retrieved under our stringent thresholds ($|\log2FC| \geq 2$, $p < 0.05$). When applying more permissive criteria ($|\log2FC| \geq 1.0$, FDR < 0.05), several of these immune mediators reappeared, indicating that their absence in the strict analysis reflects statistical cutoffs rather than biological irrelevance. This reinforces the importance of integrating multiple datasets and thresholds when interpreting transcriptomic data.

Data Sharing Statement

Datasets related to this article can be found at https://www.ncbi.nlm.nih.gov/gds, an open-source online data repository.

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Author Contibution

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no conflicts of interest in this work.

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